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CONTENTS OF PREVIOUS NUMBER

AUGUST 1946. NUMBER 2

Coronary Arteriosclerosis, Coronary Anastomoses and Myocardial Infarction: A Clinicopathologic Study Based on an Injection Method. A. Ravin, M.D., and E. F. Geever, M.D., Denver.

Fulminating Meningococcic Septicemia Associated with Adrenal Lesions: An Analysis and Discussion of Seven Cases. Lieutenant Colonel J. Murray Kinsman, Captain C. Anthony D'Alonzo and Captain Simon Russi, Medical Corps, Army of the United States.

Rheumatic Fever in Naval Enlisted Personnel: II. Effectiveness of Intensive Salicylate Therapy in Cases of Acute Infection. Commander R. C. Manchester (MC), U.S.N.R.

Changes in Hemoglobin and Total Plasma Protein After Injection of Mercurophylline. A. De Vries, M.D., Jerusalem, Palestine.

Congenital Dilatation of the Pulmonary Arterial Tree: Relation to Ayerza's Disease and Primary Pulmonary Arteriosclerosis. Michael M. A. Gold, M.D., Montreal, Canada.

Progress in Internal Medicine:

Gastroenterology: A Review of the Literature from July 1944 to June 1945 (To Be Concluded). Walter Lincoln Palmer, M.D.; William E. Ricketts, M.D., and Samuel N. Maimon, M.D., Chicago.

Book Reviews.

News and Comment.

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TROPICAL ULCERS AND CUTANEOUS DIPHTHERIA

LIEUTENANT COLONEL AVERILL A. LIEBOW

MAJOR PAUL D. MAC LEAN

LIEUTENANT COLONEL JOHN H. BUMSTEAD

AND

MAJOR LOUIS G. WELT

MEDICAL CORPS, ARMY OF THE UNITED STATES

INTRODUCTORY AND HISTORICAL NOTES

ULCERATIVE lesions of the skin occur frequently in the tropics. There is one type of ulcer, among soldiers who took part in the Pacific island campaigns, from which virulent Corynebacterium diphtheriae was often isolated. This paper is particularly concerned with lesions of this type. Typically, they are deep and have a punched-out appearance. They have been called "ecthyma" by some. This type of lesion is identical with the so-called desert sore of Northern Africa and Asia, of which the diphtheritic origin has been recognized and which frequently occurred in Allied and German soldiers. Evidence will be presented concerning the infected skin as a source of nasopharyngeal as well as cutaneous diphtheria, not only among military but also in large civilian populations to which the military have returned. Aside from these epidemiologic considerations these ulcers are of particular interest since neuritis and myocarditis are among the sequelae. There will also be presented data indicating the existence of a tremendous reservoir of diphtheria among natives in the tropics, which is largely cutaneous, which affects chiefly young children and which accounts in large measure for the remarkably accelerated acquisition of a state, in these natives, in which they do not react to the Schick test.

Other varieties of ulcerative lesions also are extremely common among natives in tropical countries. Cutaneous leishmaniasis, which may become ulcerative, is widely distributed in tropical countries but has not been described in the Solomon Islands,[1] and we have been unable to detect Leishmania bodies in any of the material derived from this region. Among natives of the South Pacific archipelagos,

From the Thirty-Ninth General Hospital.

1. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942.

Clifford James [2] has observed a common type of "tropical phagaedenic ulcer." It tends to reach a very large size and to have a deeply undermined edge and a foul necrotic base containing fusiform bacilli and spirochetes during the acute phase. The occurrence of "cocci" and "diphtheroids" is mentioned, but there were no detailed studies of the latter. James, in his description of 892 cases, noted that if the diet was low in vitamins, as it was in New Britain, the ulcers were numerous and severe and involved an earlier age group. This type of lesion has not been observed among American troops. Frequent among the latter, however, is a superficial saucer-shaped impetiginous lesion in which beta hemolytic streptococci and staphylococci are usually found. With these types of ulcers this paper will not primarily be concerned.

Diphtheria of the Skin in Temperate Climates.—In ordinary clinical practice diphtheria of the skin occurs as a complication in approximately 1 per cent of cases of nasopharyngeal diphtheria.[3] This was true in a study of 3,000 cases by Rolleston in England and in a review of approximately 2,000 by Adler at St. Anne's in Vienna, Austria. The condition was much more frequent and severe in the early part of the nineteenth century, when leeches were used in the treatment of diseases of the throat. In Rolleston's [3] series the philtrum was most commonly involved, followed by the pinna, the fingers and the external malleoli. The lesions were polymorphic but characteristically tended to become deep chronic ulcers that were resistant to treatment.

Diphtheria of the Skin in the Tropics.—In the Middle East and in Northern India diphtheritic lesions of the skin appear to have occurred frequently and out of all proportion to the amount of clinically manifest nasopharyngeal diphtheria (table 1). This has been true not only of the natives but also of the military population stationed in these districts. During the Egyptian and Palestine campaigns of World War I, Craig [4] reported finding "toxigenic" corynebacteria in 67.5 per cent of the "desert," "septic" or "Veldt" sores. The occurrence of paralysis was observed by Walshe [5] in troops evacuated from the same territory. During 1940 the condition was again prevalent

2. James, C. S.: Tropical Phagaedenic Ulcer in the Pacific, Tr. Roy. Soc. Trop. Med. & Hyg. **31**:647-666, 1938.

3. Rolleston, J. D.: Acute Infectious Diseases, London, William Heinemann, 1925.

4. Craig, C. M.: A Study of the Etiology of the "Desert," Septic or Veldt Sore Amongst European Troops and Its Association with Faucial Diphtheria, Lancet **2**:478-479, 1919.

5. Walshe, F. M. R.: Post-Diphtheritic Paralysis: Note on a Form Following Cutaneous Diphtheria, Lancet **2**:232-233, 1918.

TABLE 1.—*Cutaneous and Nasopharyngeal Diphtheria Originating in the Tropics*

	I	II	III	IV	V		VI	VII
References *	Apparent Source	Total Number of Ulcers Studied	Number Diphtheritic	Proportion of Strains from III Virulent	Other Types of Diphtheria		Proportion of Strains from V Virulent	Comment
Craig [4]	Egypt and Palestine, 1917-1918	197	129	See VII	Throat (approx.)	452	See VII	Organisms in III and V stated to be "toxigenic"
					Carriers	33		
					"Contacts"	49		
Cameron and Muir [6]	Northern Palestine, 1940	...	60	8/11	Throat	79	....	One patient in IV reported avirulent; later neuritis developed
					Nose	26		
					Carriers	78		
MacGibbon [7]	Middle East, 1943	...	3	...	Faucial	62	....	High proportion of neurologic complications (see table 9)
					Otitis	4		
					Fracture	1		
					Burn	1		
Fleck, Kellam and Klippen [9]	Middle East, 1943	Cultures of "other Veldt sores" not reported	4	See VI	Faucial	48	33/38	"Myocarditis" and "paralysis," presumably postdiphtheritic but without demonstration of bacteria
					Carriers	80	8/10	
					"Myocarditis"	1		
					"Paralysis"	6		
Bensted [15]	Northwest India, 1935	...	31	31	Faucial	15	15/15	
					Carriers	19	15/19	
Hamburger [13]	Northeast India, 1938	88	3	2/3				
Present report †	Islands of the Pacific, 1943-1944	790	174	145/173	Throat	64	60/62	See details in table 13 and figure 15
					Nose	5	5/5	
					Nose and throat	1	1/1	
					Carriers	24	12/23	

* All of these reports except that of Hamburger concern military populations. In Burma many soldiers with diphtheritic ulcers have been carefully studied by C. S. Livingood and his co-workers (personal communication).

† In column V are included all cases in which organisms were found in the nasopharynx.

among British troops stationed in Palestine and was thoroughly investigated by Cameron and Muir.[6] A more recent report concerning diphtheria in the British army of the Middle East was presented by MacGibbon,[7] who likewise noted the disproportionately large numbers of cutaneous lesions and remarked about how often the disease is missed. It was also observed among returned soldiers by Williams.[8] Four cases of diphtheritic "Veldt" sore were found, together with 48 cases of pharyngeal diphtheria, by Fleck, Kellam and Klippen[9] among German prisoners of war captured in Africa and confined to a prison camp at Aliceville, Ala. In Algeria,[10] from August to September 1943, there was an epidemic of 4,000 cases of tropical ulcer, the cause of which was stated to be unknown. Whether adequate cultures were made to detect C. diphtheriae was not stated.

Northern India appears to be another great endemic center of cutaneous diphtheria. Epidemics of tropical ulcers are said to have "swept like a plague" through Assam.[11] Diphtheritic sores have been described among natives of the Chittagong hills,[12] and Hamburger[13] found 3 per cent of the ulcers in a neighboring district to contain C. diphtheriae. Grindlay[14] observed them in troops fighting in the adjacent Burmese jungle but considered them to be associated with spirochetal infections and vitamin deficiency, although no detailed etiologic investigations were reported. On the other side of Northern India, in the "Northwest Frontier Province," diphtheritic ulcers and the associated conditions that were prevalent among soldiers in British regiments were carefully studied by Bensted.[15]

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6. Cameron, J. D. S., and Muir, E. G.: Cutaneous Diphtheria in Northern Palestine, Lancet **2**:720-723, 1942.

7. MacGibbon, T. A.: Diphtheria in the Middle East: Some Observations on Seventy-One Cases, Edinburgh M. J. **50**:617-625, 1943.

8. Williams, H. C. M.: Cutaneous and Conjunctival Diphtheria, Brit. M. J. **2**:416-417, 1943.

9. Fleck, S.; Kellam, J. W., and M. Klippen, A. J.: Diphtheria Among German Prisoners of War, Bull. U. S. Army M. Dept., 1944, no. 74, pp. 80-89.

10. Epidemic of Tropical Ulcer in Algeria, Bull. U. S. Army M. Dept., 1944, no. 75, pp. 13-14.

11. Diphtheria, Bull. U. S. Army M. Dept., 1944, no. 76, p. 21.

12. Pasricha, C. L., and Panja, G.: Diphtheritic Ulcers of the Skin: The "Garigha" of Chittagong Hill Tracts, Indian J. M. Research **27**:643-650, 1940.

13. Hamburger, H. J.: Observation on the Pathology and Therapy of the So-Called Frontier Sore, Indian M. Gaz. **74**:151-155, 1939.

14. Grindlay, J. H.: Treatment of Skin Infections in the Assam-Burma Jungle, Bull. U. S. Army M. Dept., 1944, no. 74, pp. 74-80.

15. Bensted, H. J.: A Limited Outbreak of Diphtheria Exhibiting Both Cutaneous and Faucial Lesions, J. Roy. Army M. Corps **67**:295-307, 1936.

The lesions described by these writers bear remarkable resemblance to the deep, "punched-out" type of tropical ulcers seen by us in troops evacuated from the Solomon Islands, Saipan (one of the Marianas) and Leyte (one of the Philippine Islands).

MATERIALS AND METHODS

General Phases.—The earlier investigations of the ulcers were made at the Thirty-Ninth General Hospital from March 1943 to July 1944, during which time the ulcers of 85 patients were recognized as diphtheritic and studied. Most of the patients were derived from the Twenty-Fifth and Forty-Third Divisions. The second phase was carried out from Sept. 15 to Oct. 31, 1944 in the New Hebrides with the Twenty-Seventh Division shortly after the evacuation of the division from the Saipan campaign. During this interval the diphtheritic tropical ulcers of 89 patients were studied. A survey was made of the incidence of the ulcers, of the diphtheria carrier rates and of other pertinent data in these divisions during rest periods. At the same time preliminary investigations were carried out on Tonkinese and Melanesian natives of these islands in pursuit of early studies on the results of the Schick test among adult Solomon Islanders. Later, in the Marianas, these were amplified among the Chamorros. Then also came the opportunity for confirmatory observations on soldiers evacuated from Leyte.

Types of Investigation.—During the earlier part of the study, from March to September 1943, intensive parasitologic and bacteriologic studies were made, including anaerobic cultures, dark field examinations, potassium hydroxide smears and cultures for fungi and Giemsa stains for protozoa. Leishmania bodies in particular were searched for both in the Thirty-Ninth General Hospital and in the Saipan groups. Neither protozoa nor spirochetes were found, and fungi, such as Monilia and Epidermophyton, were only rarely encountered. When the frequent presence of C. diphtheriae became apparent, a special procedure was employed to obtain evidence concerning the epidemiologic aspects of lesions associated with this organism and the pathogenesis of these lesions, and the bacteriologic methods were simplified to concentrate on the detection of the organism.

A standard form of clinical record was used in each instance, which included questions concerning the patient's home and military history, with special emphasis on any exposure to diphtheria (sore throats and ulcers occurring in the organization), previous Schick test, record of immunization, or sore throat occurring in the patient himself, and questions designed to elicit evidence of neurologic damage and also the mode of origin and the course of the ulcer to the time of the patient's admission to the hospital. In each instance the size of the lesion at the time of admission was recorded, and follow-up data under various modes of treatment were collected. Cultures of material taken from the ulcers were made at intervals, and cultures of material taken from the nose and the throat were made routinely. The Schick test was made in all instances except those in which concurrent nasopharyngeal diphtheria demanded the immediate administration of antitoxin. Before the patient was discharged from the hospital, a physical examination, with emphasis on the neurologic aspects, was again performed. It is the review of these systematic records that is the basis of the tables presented in the text.

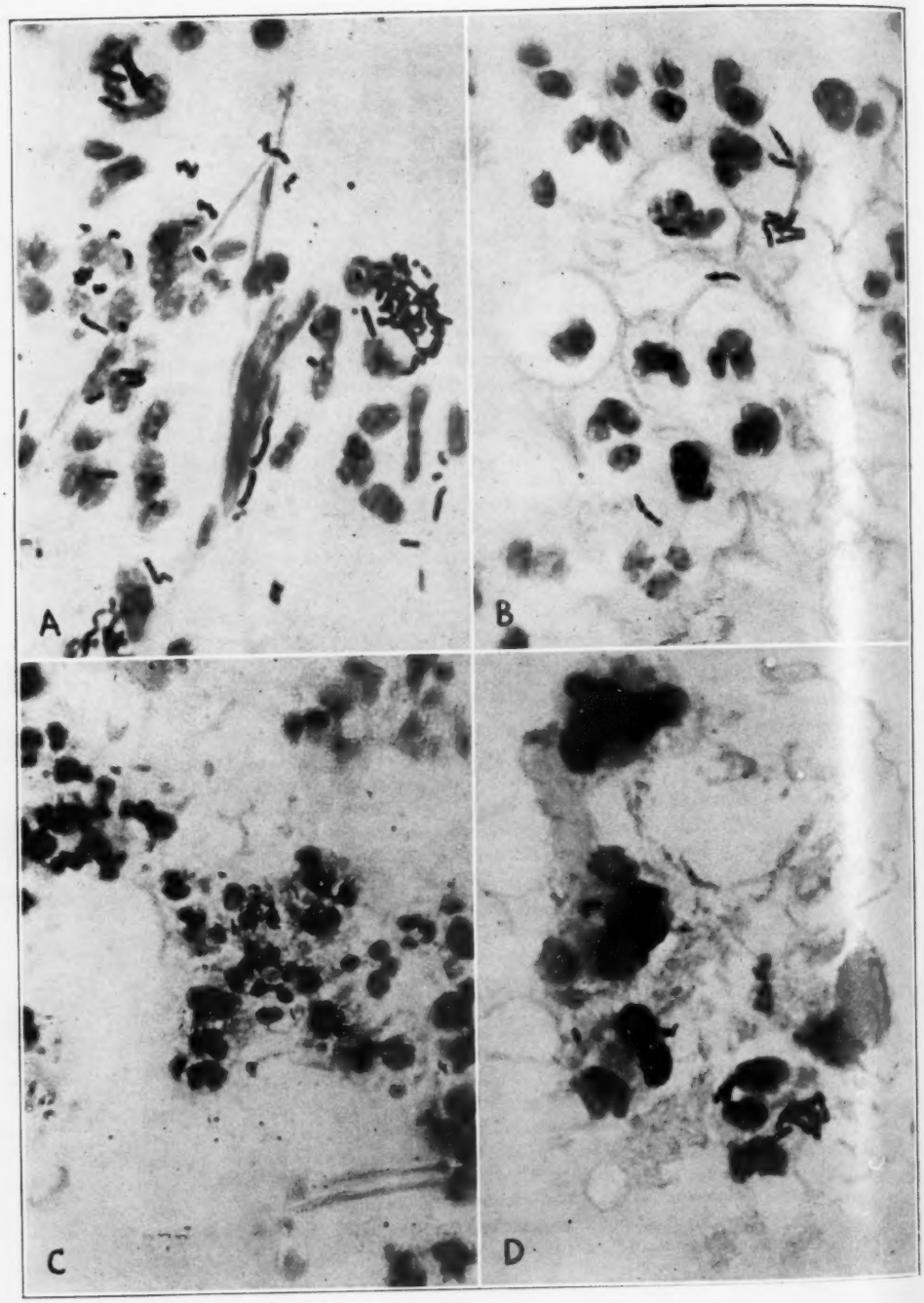

Figure 1

(See legend on opposite page)

Methods of Culture and Identification of C. Diphtheriae.—The simplest methods of culture are effective. If the ulcer is relatively clean and not crusted, material for culture may be taken from the base directly, without further preparation; it is unnecessary to apply alcohol or other agents. In hospital cases, as a routine procedure, it is more satisfactory to apply a warm pack of isotonic solution of sodium chloride to the lesion for from three to twenty-four hours, which helps to remove any excess of exudate, fibrinous crust, or residue of ointments that may previously have been applied. Exudate is then removed from the base of the ulcer for smear and culture. Löffler's serum slants or blood agar may be used as mediums. Tryptose agar without dextrose,[16] containing 5 per cent human blood, was employed.

In direct smears from the lesions the organisms identified as C. diphtheriae, as a rule, are differentiable from diphtheroids, since they are longer, more pleomorphic, with slender and club-shaped forms, more granular and less intensely gram-positive. They are often found within the polymorphonuclear leukocytes of the exudate (fig. 1). Sometimes they are extremely numerous and are the predominant element of the bacterial population, but usually there is an admixture of gram-positive cocci in chains and clumps. In exudates the organisms frequently are stouter than in the classic descriptions, which are based on the appearance of the bacteria on Löffler's medium after twelve to twenty-four hours of cultivation. The bacteria from the cutaneous lesions assume the classic forms when grown on this material.

With the Saipan group an attempt was made to determine how well purely morphologic criteria when applied by an experienced observer would bear the test of subsequent bacteriologic investigation. In smears of exudate from 150 ulcers the presence or the absence of C. diphtheriae was correctly diagnosed one hundred and twenty-five times (83.3 per cent). In 10 instances (6.6 per cent) Klebs-Löffler bacilli were not seen on direct smears but were found on cultures. In 15 instances (10 per cent) gram-positive pleomorphic bacilli were incorrectly diagnosed as C. diphtheriae from the smear. This demonstrates that with experience a reasonably accurate guess can be made which may have application under field conditions when facilities for culture are not available.

In smears made from the Löffler serum slant after eight to twelve hours of incubation C. diphtheriae appears in long slender pleomorphic forms which make

16. Manual of Dehydrated Culture Media and Reagents, Detroit, Difco Laboratories, Reprint, 1941, p. 91.

EXPLANATION OF FIGURE 1

A (patient Y56), exudate from diphtheritic ulcer. Many of the pleomorphic toxigenic bacilli are intracellular. × 1,100.

B (patient Y56), exudate from another ulcer. Note "double suppository" forms of C. diphtheriae sometimes observed in direct smears of exudates. × 1,100.

C (patient Y57), exudate from diphtheritic ulcer. C. diphtheriae is seen within the leukocytes. See figure 14, *A*. ×500.

D (patient Y57), exudate from diphtheritic ulcer. Note intracellular position of pleomorphic gram-positive bacilli. × 1,100.

In this and subsequent legends Y in the designation of the patient means that the lesion developed in the Solomon Islands, and S, that it developed in Saipan.

it possible to differentiate them tentatively from the generally much shorter and thicker diphtheroids, pending the results of the other tests. In our experience a positive preliminary reading of the slant was sufficiently reliable to warrant isolating the patient.

Although the technic[17] of isolating C. diphtheriae is exceedingly simple, certain precautions should be employed. The use of blood agar plates is advantageous, since the isolated colonies can be studied and picked for subculture within twenty-four hours. The essentials of the technic are:

1. The p_H of the agar must be adjusted to 7.6 before sterilization. C. diphtheriae grows much better on slightly alkaline mediums.
2. The medium must be cooled to 45 C. or less before the blood is added. If the blood is overheated, the narrow ring of hemolysis characteristic of C. diphtheriae mitis may be obscured, and the colonies are then less easily distinguished from those of staphylococci and diphtheroids.
3. Good streaking technic must be employed.

This method is sensitive and accurate only if well isolated colonies are obtained. The best method for learning to identify these organisms is to study known strains at various intervals in comparison with staphylococci and diphtheroids which offer the greatest difficulty in gross recognition of the colonies. On the blood agar plate C. diphtheriae is easily distinguished from certain hemolytic corynebacteria that are commonly observed among troops and natives in the tropics. These probably belong to the Corynebacterium ovis and Corynebacterium pyogenes group and are the subject of a separate report. The designation "Corynebacterium hemolyticum" has tentatively been applied to this organism. On Löffler's medium the organism closely resembles C. diphtheriae, but on blood agar plates during the first twenty-four hours the colonies of C. hemolyticum come to be surrounded by a large zone of beta hemolysis which renders them easy to identify.

All the strains of C. diphtheriae mitis that were tested, a total of 91 from patients with cutaneous diphtheria and 49 from patients with nasopharyngeal diphtheria and carriers, fermented dextrose. Maltose was usually fermented within twenty-four hours, but with some of the strains there was complete or partial reversion of the medium to alkalinity by the end of the week. Most of these strains fermented galactose at least partially, and the reversion phenomenon was observed in a few. Sucrose broth in rare instances showed a transient slight reduction in p_H of the medium (not below 7.0) but became strongly alkaline by the fourth to the seventh day. Transient acidity (not below p_H 6.8) also developed in lactose broth. These fermentation reactions occurred whether or not the strain was toxigenic.

All strains were tested for toxigenicity by the controlled intracutaneous method of Fraser and Weld,[18] using the guinea pig and in some instances the rabbit being used. The results obtained by this method were unequivocal. All organisms found to be atoxic were tested again. The results of the second examination invariably agreed with the first.

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17. Hewlett, R. J.: Corynebacterium Diphtheriae and Diphtheroid Organisms, in Bulloch, W., and others: A System of Bacteriology in Relation to Medicine. Medical Research Council, London, His Majesty's Stationery Office, 1930, vol. 5, pp. 67-150.

18. American Public Health Association: Diagnostic Procedures and Reagents, New York, American Public Health Association, 1941.

Correlation of Morphologic and Cultural Characteristics with Toxigenicity.—Considering strains from the tropical ulcers, 84.1 per cent of the strains of hemolytic corynebacteria with these morphologic and colonial characteristics and fermentative powers proved toxigenic. By generally accepted definition the remaining 15.9 per cent must be considered as C. diphtheriae, nontoxigenic. The atoxic strains were relatively more common in carriers (table 13). We did not encounter any of the nonhemolytic gravis[19] strains. All the many strains of nonhemolytic corynebacteria that were studied by us (44 strains) proved to be nontoxigenic. Two of these had the fermentative but not the morphologic properties of C. diphtheriae.

TABLE 2.—*Bacterial Flora of "Tropical Ulcers" and of Certain Other Dermatitides (790 Patients)* *

Organism	27th Division (288 Patients)	25th and 43d Divisions †	
		Group A (278 Patients)	Group B (224 Patients)
Corynebacterium diphtheriae, toxigenic	75	65	5
Corynebacterium diphtheriae, nontoxigenic	13	6	9
"Diphtheroids"	18	69	49
Hemolytic corynebacteria of Corynebacterium pyogenes group	9	21	19
Beta hemolytic streptococcus	145	126	133
Staphylococcus albus	28	138	100
Staphylococcus aureus	183	99	132
Alcaligenes faecalis	22	18	35
Escherichia coli	0	11	2
Alpha streptococcus	9	6	3
Gamma streptococcus	0	6	0
Pseudomonas pyocyanea	4	5	7
Proteus vulgaris	1	3	2
Neisseria catarrhalis	0	0	1
Unidentified gram-negative bacillus	0	0	2
Percentage containing Corynebacterium diphtheriae	30.6	25.5	6.2
Percentage containing toxigenic Corynebacterium diphtheriae	26.0	23.4	2.2

This table refers to all ulcerative dermatitides of the skin. Information concerning the proportion of these having the morphologic aspects of the typical "tropical ulcer" or ecthyma, which is the main subject of this report, is available only for the Twenty-Seventh Division and is presented in the text.

* Results of first examination of each patient are recorded.

† For definition of groups see text.

BACTERIOLOGIC AND MORPHOLOGIC ASPECTS OF TROPICAL ULCERS

Bacteriologic Observations.—A list of the bacteria present in all ulcerative and moist desquamative cutaneous lesions of which the bacterial flora was ascertained is presented in table 2. Many of these were of the shallow or impetiginous type and were not classed as typical of the diphtheritic ulcer as described in the next section. The relationship between the morphologic and the bacteriologic aspect is

19. Anderson, J. S.; Happold, F. C.; McLeod, J. W., and Thomson, J. G.: On the Existence of Two Forms of Diphtheria Bacillus—B. Diphtheriae Gravis and B. Diphtheriae Mitis—and a New Medium for Their Differentiation and for the Bacteriological Diagnosis of Diphtheria, J. Path. & Bact. **34**:667-681, 1931.

considered in a later section. In table 3 is recorded the bacterial flora of those lesions in which C. diphtheriae was actually found.

It is interesting to note that the shorter the interval between the time that the lesion is acquired and the time that it is cultured the higher the incidence of C. diphtheriae and the greater the ratio of toxigenic to atoxic bacilli. This relationship is brought out in table 2. In it the Thirty-Ninth General Hospital series has been subdivided into two groups. Group A represents the patients studied before Feb. 15, 1944 and comprises largely members of the Twenty-Fifth

TABLE 3.—*Bacterial Flora of Diphtheritic Ulcers of the Skin (Primary Isolations)*

	Corynebacterium Diphtheriae (Pure Culture)	Corynebecterium Diphtheriae (4 Plus or 3 Plus)	Associated Bacteria				
			Diphtheroids	Beta Hemolytic Streptococcus	Corynebacterium Hemolyticum	Staphylococcus Albus	Staphylococcus Aureus
C. diphtheriae, toxigenic (total, 145).....	6	84	6	68	14	45	49
C. diphtheriae, nontoxigenic (total, 28).....	..	16	1	13	5	9	13

Numbers refer to patients.
The data have been subdivided according to toxigenic and nontoxigenic strains.
"4 Plus or 3 Plus" refers to predominance of the bacteria.

TABLE 4.—*Type of Lesion from Which C. Diphtheriae Was Cultivated*

Lesion	C. Diphtheriae	
	Virulent	Avirulent
Deep ulcers	114	17
Shallow ulcers or impetiginous lesions	17	8
Deep tract	4	..
Diffuse desquamative and ulcerative dermatitis	4	..
Paronychia *	2	..
Total †	141	25

* In another patient paronychia complicated a diffuse desquamative and ulcerative dermatitis (patient Y 5, fig. 74).

† No exact data concerning the morphologic character of the lesions are available in 8 of the earlier cases.

Division. This group came to the rest area during November 1943, approximately six weeks after cessation of combat (when most of the ulcers were acquired). Group B consists largely of members of the Forty-Third Division evacuated to the rest area after Feb. 15, 1944, some twenty weeks after their combat experience. The Twenty-Seventh Division group is comparable to group A, in that the studies were carried out some four to six weeks after the Saipan campaign.

The decrease in the proportion of toxigenic to atoxic strains of C. diphtheriae with time is of interest. In the Thirty-Ninth General Hospital group, 40 of 43 (93 per cent) diphtheritic ulcers of less

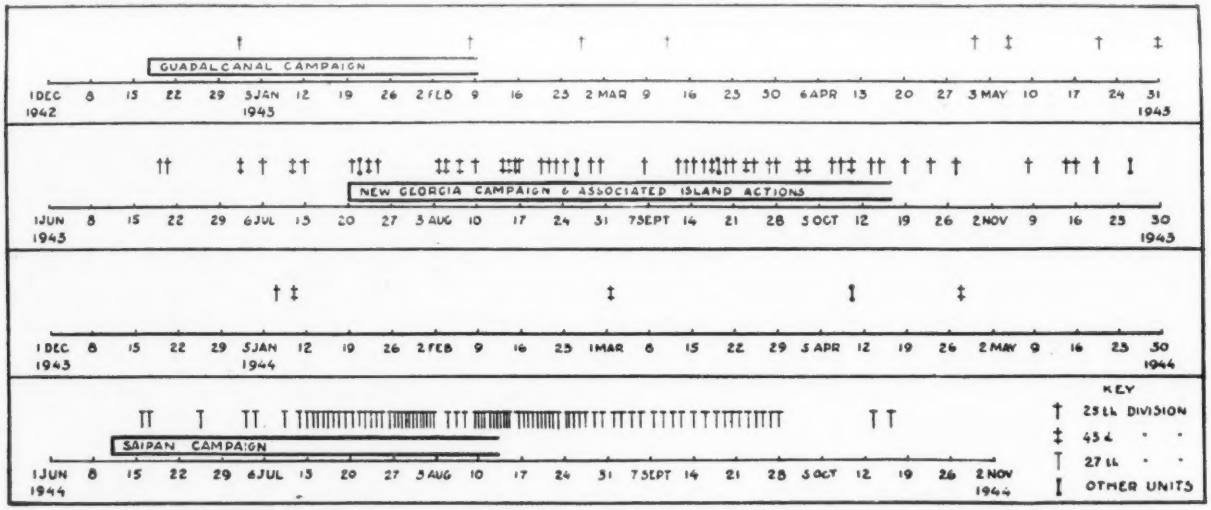

Fig. 2.—Diphtheritic tropical ulcers. Onset in relation to the campaigns. The dates of onset of the ulcers as estimated by the patients are represented. There are certain inaccuracies; e. g., the clinical records of 2 patients indicated that the disease began on a certain island before that island was actually taken by the troops. These are nevertheless represented on the chart on the date indicated by the patients' statement. It is obvious, therefore, that some of the dates of onset should be shifted to the right.

The data are incomplete in the following respects:

1. All patients evacuated during and after the Guadalcanal campaign until approximately March 13, 1943 (and some after this date) went to other installations. The first section of the chart is therefore included only for the purpose of reference.
2. The records of some of the earlier patients are incomplete.
3. Systematic cultures of all ulcerative lesions of the skin were not made in this hospital until June 1943.
4. Many patients evacuated during action in New Georgia likewise never reached this installation.
5. With regard to the Twenty-Seventh Division, all the information charted is based on cases coming to notice after the arrival of the troops in a distant rest area. A systematic study was performed as outlined in the section entitled "Associated Clinical Observations." Some patients were hospitalized on Saipan and were lost to the present series.

Despite these defects, the relation of the onset of the ulcers to the conditions of combat is obvious and would doubtless be even more striking were it possible to trace every case. Those ulcers occurring in the Forty-Third Division before the beginning of the New Georgia campaign are examples of the sporadic form of the disease occurring among troops in training or in garrison.

The cases in which diphtheritic infection was spread by contact in the Thirty-Ninth General Hospital are not charted.

than twelve weeks' duration contained toxigenic organisms, whereas of 25 older ulcers only 17 (68 per cent) contained toxigenic bacilli. The strains of C. diphtheriae obtained by Pasricha and Panja [12] from the extremely chronic ulcers of the Indians of Assam were all atoxic for the guinea pig, and the strains isolated by us from Tonkinese, Melanesian and Chamorro natives were also usually atoxic for the guinea pig. One strain recovered from an ulcer of a patient (Y1) on Nov. 18, 1943 was toxigenic in contrast to one morphologically and biochemically similar obtained on Jan. 28, 1944 from a recurrence. In the Saipan group 2 to 3 colonies from the primary plate were tested in 5 instances to determine whether both toxigenic and atoxic strains might coexist, but the various strains were all toxigenic. In our experience toxigenicity was not lost in vitro when a series of organisms was stored on blood agar for as long as fourteen months with only one intervening transplantation. These observations indicate that the longer C. diphtheriae persists in the body the less likely is the recovered strain to be toxigenic. The mechanism of this is not clear, but it probably depends on the formation of atoxic variants.[20]

The existence of another virulence factor is suggested by an observation of Pasricha and Panja.[12] They found that the nontoxigenic, but otherwise typical, C. diphtheriae when injected into the human skin produced ulcers resembling those of the patients from whom the organisms had been obtained, whereas diphtheroids similarly inoculated were totally innocuous. The Schick reactions of their experimental subjects were not stated.

Development and Appearance of the Typical Lesion.—Despite the wide geographic diversity in stations of the various divisions—Solomon Islands, the Marianas, and Philippine Islands—the ulcers observed among these divisions were remarkably similar. They were also similar to the cutaneous diphtheria of the temperate zones, to the "desert" or "Veldt" sores of Libya and Palestine (compare figures in Cameron and Muir [6]), to the "Garigha" of Northern India and to those of the natives and Tonkinese in the New Hebrides and the Chamorros of the Marianas. In the majority of instances the onset of the ulcer was incident to actual combat or patrol activity and was uncommon in resting troops (table 5 and fig. 2). Usually (in 55 per cent of the cases) there was a definite history of trauma or insect bite (table 6). In such cases the initial lesion, for example a scratch, began enlarging instead of healing. The base, originally linear, became increasingly broad and covered with exudate. The lesion deepened, and the edges, at first red and edematous, became "rolled" as scar tissue formed. Characteristically, granulations failed

20. Dudley, S. F.; May, P. M., and O'Flynn, J. A.: Active Immunization Against Diphtheria, Medical Research Council, Special Report Series, no. 195. London, His Majesty's Stationery Office, 1934.

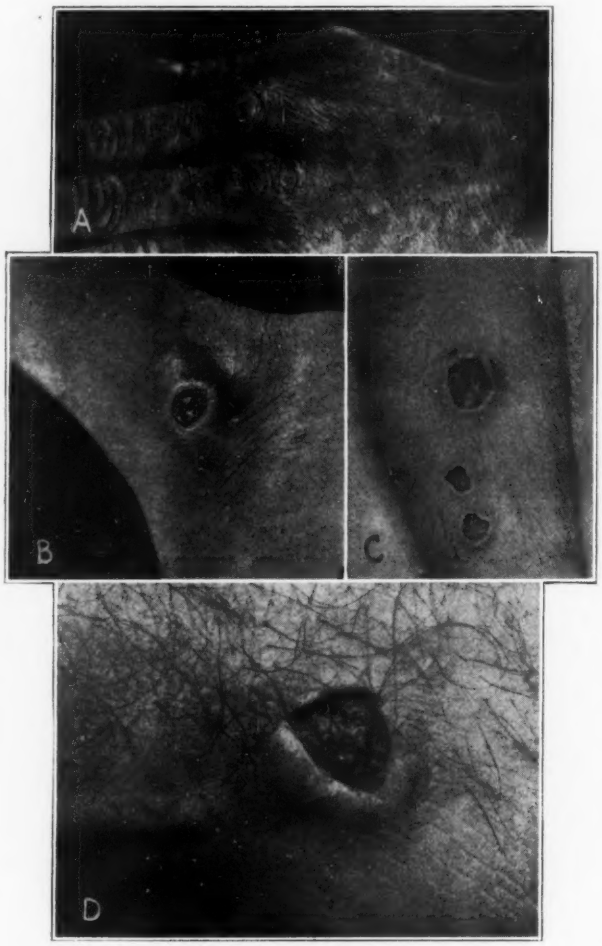

Fig. 3.—All illustrations are of lesions found to contain toxigenic C. diphtheriae except as noted in legends. A very high proportion of atypical diphtheritic lesions are illustrated. Those shown in *B*, *C* and *D* and in figure 12 *A* are typical of most diphtheritic ulcers. Patients labeled Y are from the Solomon Islands. Those labeled S are from Saipan. *A* (patient Y52), lesion appears insignificant, but there is deep penetration beneath the scab. Toxigenic C. diphtheriae was grown from the exudate.

B (patient Y40), typical chronic ulcer, of four weeks' duration. There is bronze-violaceous pigmentation of the surrounding skin.

C (patient Y43; see fig. 4 *B*), ulcers of leg (photograph of a water color by Private First Class S. L. Abbot).

D (patient S52)), close-up of a typical ulcer of a hand, eight weeks in duration. There is a relatively clean base with only a slight amount of adherent fibrinopurulent material (photograph by United States Army Signal Corps).

to rise but were continuously necrosed at the bottom. Thus the originally linear lesion tended to become rounded or serpiginous, extremely indolent and resistant to treatment in the field.

The diphtheritic lesions were usually multiple (75 per cent) and situated on the extremities (99 per cent). The high incidence of lesions on the feet makes the ulcers frequently disabling. In other locations they are rarely painful and usually cause little inconvenience to the hardy soldier. The lesions varied in size, the largest observed

TABLE 5.—*Islands Where Lesions Were First Noted*

Location	C. Diphtheriae	
	Virulent	Avirulent
Guadalcanal	21	8
New Georgia	18	4
Vella Lavella	5	..
Kolombangara	5	..
In transit to or at New Zealand	9	1
Saipan	63	10
In transit to or at the New Hebrides *	14	3

Incidence on the various islands obviously is governed in part by military movements.

There were also 8 patients, not included in the general series, in whom there developed proved diphtheritic ulcers of typical appearance on Leyte.

* One patient from the Forty-Third Division; others from the Twenty-Seventh Division.

TABLE 6.—*Mode of Onset*

Lesion	C. Diphtheriae	
	Virulent	Avirulent
Following trauma or insect bites	66	23
De novo	30	1
As "small pimples"	14	1
In diffuse dermatitis	4	..
In preexisting epidermophytosis	4	1
As "blisters"	3	1
As pustules	2	..
As paronychia	2	..
Post fellationem	1	..
Total	126	27

by us measuring 45 by 40 mm. (case S12). Occasionally a very minute, but otherwise typical, lesion was found to be diphtheritic (fig. 3*A*).

The characteristic lesions were rounded, deep and "punched out" but did not extend into the subcutaneous tissue (fig. 3*B*, *C* and *D*). Of the lesions harboring C. diphtheriae 84.1 per cent had this appearance. The margins were declivitous, indurated and often "rolled." Occasionally they were slightly undermined. Usually there was a zone of induration, erythema and violaceous pigmentation about the sharply defined sore (fig. 3*B*). The base was usually relatively clean, but sometimes it had some adherent soft fibrinopurulent material or a dried fibrinous crust. The exudate beneath the crust was gray or

gray-green rather than yellow. Occasionally there was a gray-green fibrinous membrane that was impossible to scrape from the surface (fig. 4).

Atypical Lesions.—In 4 instances in which the condition developed in preexisting epidermophytosis of the feet the lesion became a deeply penetrating narrow tract with thick everted lips (fig. 5), resembling those of the cutaneous ulcers seen elsewhere. In 1 case the opening of such a deep tract was minute. It exuded gray seropurulent material and was the source of discomfort entirely disproportionate to its size.

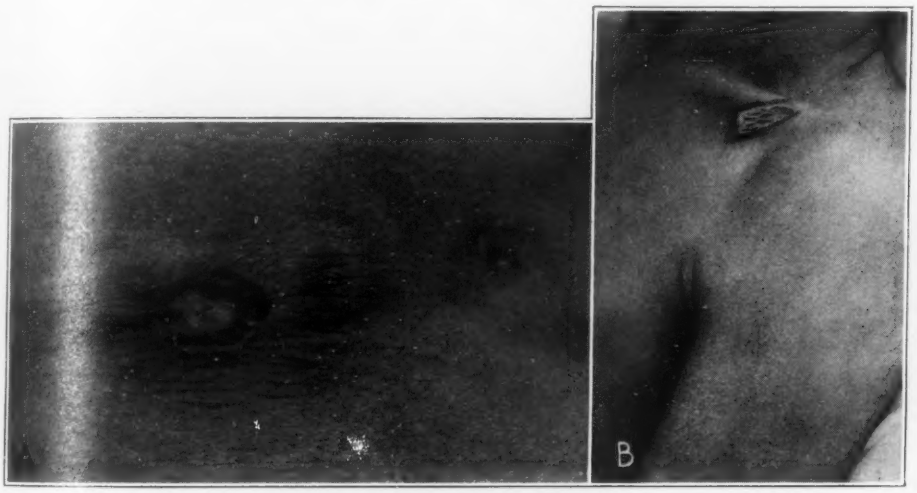

Fig. 4.—*A* (patient S25), diphtheritic ulcer in skin over the left iliac crest, three weeks after onset. It is a relatively shallow but punched-out lesion, with an adherent gray-green membrane at the base.

B (patient Y43), ulcer of skin over the clavicle, with adherent green membrane (photograph of a water color by Private First Class S. L. Abbot).

Any unexplained sinus tract of the feet in soldiers evacuated from the tropics should be suspected of being of diphtheritic origin.

Occasionally C. diphtheriae was demonstrated in shallow ulcers or in impetiginous dermatitis (table 4). In 4 instances there was a diffuse moist desquamative and ulcerative dermatitis (fig. 6). One of these (fig. 7 *A*) had multiple paronychias. A wardman attending a patient with diffuse diphtheritic dermatitis had an extremely chronic diphtheritic paronychia of two fingers (fig. 7 *B*).

Some of the shallow ulcers had relatively short histories (fig. 8) and may represent a relatively "acute" stage of the diphtheritic ulcer.

Nevertheless, characteristic deep ulcers can develop in as short a time as one month. This is illustrated by case Y40 (fig. 3 *B*).

Occasionally the lesions were unusual in location, as in the penis (fig. 9) or in the perianal region (fig. 10).

Fig. 5 (patient S11).—Epidermophytosis superinfected with C. diphtheriae. The indurated rolled edge and the deep cavity are characteristic of diphtheritic ulcers in this region.

Fig. 6 (patient Y65).—Moist desquamative and ulcerative dermatitis. Virulent C. diphtheriae was isolated from the scalp and from ulcers of a leg.

Relationship of Bacteriologic and Morphologic Findings.—With regard to only those lesions which actually contained toxigenic C. diphtheriae (table 4), 118 of 141 (84 per cent) had the typical punched-out character as described in the preceding section. Sixty-eight per cent of the lesions containing atoxic C. diphtheriae had this appearance.

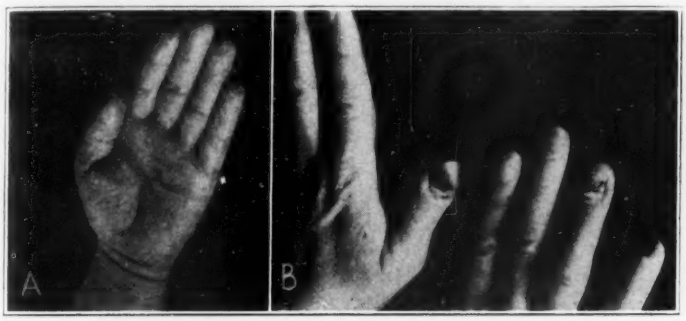

Fig. 7.—*A* (patient Y5), moist desquamative dermatitis of the upper extremities with ulcers of the legs. Note multiple paronychias. C. diphtheriae was present on the skin of the palms and in the paronychias. The duration was six weeks. *B* (patient Y20), diphtheritic paronychias. Patient was a wardman who took care of an officer (Y68) with a lesion resembling that shown in figure 6.

Fig. 8 (patient Y21).—Crusts adherent to acute relatively superficial ulcers. See section on complications, group A, in text, for details of the history.

With regard to the Saipan group an attempt was made to predict from the clinical appearance of the lesion, before the results of culture

became available, whether or not it would contain C. diphtheriae. A correct prediction of whether or not the ulcer would be found to harbor the C. diphtheriae was made in 69.1 per cent of attempts at judging 191 ulcerative lesions.

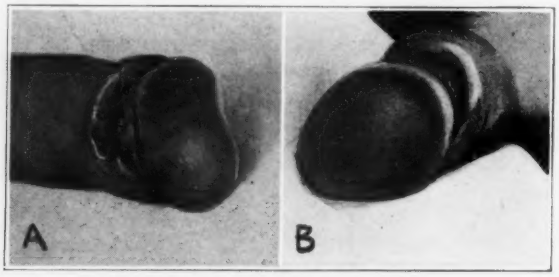

Fig. 9.—*A* (patient Y53), acute diphtheria of coronal sulcus, beginning four days post fellationem.

B (patient Y6), lesion resembling chancre in its firmness but with an adherent green membrane at its base from which virulent C. diphtheriae was isolated. The patient had just returned from the tropics and had not had sexual intercourse for more than one year (photographs of water colors by Private First Class S. L. Abbot).

Fig. 10 (patient Y29).—Ulcer resembling a pilonidal sinus. Note kissing ulcer at the right. C. diphtheriae was isolated from ulcer of the ankle an Oct. 8, 1943. The patient had diphtheritic neuritis, and spinal fluid proteins totaled 93, mg. per hundred cubic centimeters on December 27.

This suggests that in the age group concerned and in the territory under consideration it is C. diphtheriae that plays the important role

in giving the lesions their characteristic morphologic stamp, although no claim is made that the lesion is pathognomonic.

C. diphtheriae is not always found in lesions considered typical (fig. 11). In the Saipan group 98 of 191 ulcers were thought clinically to be typical but only 52 (53 per cent) of the 98 actually yielded C. diphtheriae on culture. One explanation is that C. diphtheriae has, in time, been replaced by other organisms. This possibility is supported by the data in table 2, as discussed previously. An analogous statement may be that the shovel which dug the ditch is no longer there.

Fig. 11 (patient M.).—Typical ulcers, much treated and partly healed. No C. diphtheriae was isolated (two attempts). The patient had diphtheritic neuritis (spinal fluid proteins, 170 mg. per hundred cubic centimeters on Nov. 17, 1943). Tachycardia was noted with changes in the electrocardiogram.

ASSOCIATED CLINICAL OBSERVATIONS

Distant Effects.—Despite the frequent presence of the beta hemolytic streptococcus (table 3), it was remarkable that lymphangitis and lymphadenitis were noted in only 2 patients.

Aside from the occasional presence of neuritis there were usually no general symptoms of intoxication where the ulcers alone were the seat of C. diphtheriae. In rare instances there was unexplained tachycardia. One of the patients (Y56; figs. 12 and 13) had a persistent elevation of the pulse rate, on occasion as high as 120, on complete rest in bed without fever or changes in the electrocardiogram. The tachycardia disappeared as the ulcers healed.

In 2 patients with positive Schick reactions a striking erythema and edema occurred about the ulcers on the day following the administration of diphtheria antitoxin. This may be analogous to the Francis reaction as observed in pneumococcic infections.

Relation to the Schick Reaction.—The relation of the incidence of the lesion to the Schick reaction of the person is of considerable interest, as it may have bearing on prevention. Bensted,[15] during the outbreak of diphtheria in British troops in Northwest India, performed Schick tests on members of his battalion. After this he observed that all those in whom diphtheritic ulcers developed had positive Schick reactions. Both the faucial and the cutaneous lesions ceased with the development of immunity following the administration of diphtheria toxoid-antitoxin floccules.[21] These observations are insufficient in scope to indicate that the skin of a person who does not react to the Schick test cannot become infected with C. diphtheriae. In the case of the Twenty-Seventh Division the Schick test was performed on a considerable number of persons during their stay in the rest area. In 1 instance a state in which no reaction could be observed with the test was known to antedate the development of a diphtheritic ulcer. The patient

TABLE 7.—*Schick Reactions of Persons with Diphtheritic Tropical Ulcers*

Group	Patients with: Ulcers Containing Toxigenic C. Diphtheriae — Number Tested	Ulcers Containing Toxigenic C. Diphtheriae — Per Cent Positive	Ulcers Containing Atoxic C. Diphtheriae — Number Tested	Ulcers Containing Atoxic C. Diphtheriae — Per Cent Positive	Per Cent Positive Reactors in Division
Thirty-Ninth General Hospital	57	42.1	14	28.5	25th Division, 21% of 9,000 men; 43d Division 27.8% of 11,968 men
Twenty-Seventh Division.....	74	20.3	12	8.5	11.0% of 12,135 men

had been tested one month before admission, and the ulcer was of two weeks' duration. An isolated instance is, however, insufficient to establish the point because of the possibility of error. The most significant evidence that the Schick reaction has bearing on the development of the ulcers is that the percentage of patients with diphtheritic ulcers who react positively to the test is approximately twice that of persons who react positively in the group as a whole (table 7).

The existence of a state in which no positive Schick reaction can be obtained in persons with diphtheritic ulcers can be interpreted to mean either that the organisms resident in the skin have produced immunity or that the ulcers developed in persons in whom a positive Schick reaction was not obtainable. The question of whether the skin of a person who does not react to the Schick test can become infected will not be solved until a sufficiently large number of persons with known

21. Diphtheria toxoid-antitoxin floccules is prepared by treating the filtrate with formaldehyde and then proceeding as for toxin-antitoxin floccules which is prepared by adding diphtheria antitoxin to the filtrate in the proportion necessary to produce suitable flocculation separating the floccules and washing and suspending them in isotonic solution of sodium chloride.

Schick reactions have been studied. This information may be forthcoming by examination of the case records of the men who have already been tested before entering combat in the tropics.

Certain patients have positive Schick reactions despite the fact that ulcers containing toxigenic C. diphtheriae have existed for many months. This suggests that the skin is not a good absorbing surface for the toxin. However, with respect to pharyngeal diphtheria it has been long known that a single attack fails to reverse the Schick reaction in about 60 per cent of patients as tested three to four months after recovery.[22] Further evidence that the skin does not absorb toxin as well as the pharynx is the long latent period before neuritis developed in the patients whose lesions were purely cutaneous.

The Schick reactions of persons with peripheral neuritis and the relation to therapy are discussed in a later section.

Cutaneous and Extracutaneous Diphtheria in the Same Person.—Previous observers have noted the occasional concomitance of cutaneous and extracutaneous diphtheria (table 8). Routine cultures of material

TABLE 8.—*Corynebacterium Diphtheriae Occurring Concomitantly in the Skin and Elsewhere in the Same Persons*

Reference	Number of Ulcers	Patients			Carriers		
		Faucial	Nasal	Faucial and Nasal	Faucial	Nasal	Faucial and Nasal
Houston [15]	31	2	..	..	..	..	..
Cameron and Muir [9]	66	8	4	3	3	4	3

from the noses and the throats of the 174 patients with diphtheritic ulcers have demonstrated C. diphtheriae in 19 of them. Ten of these clinically had pharyngeal diphtheria and 2 fibrinous rhinitis. There were also 6 pharyngeal carriers, and 1 was a nasal carrier.

The 12 clinical cases are of particular interest. In 3 of them the patients (Y8, Y27 and Y28) had been sent to the hospital for the treatment of the ulcers and were found to have positive Schick reactions at the time of admission. The acute pharyngitis developed while the patients were in strict isolation for periods varying from two and a half to five weeks. In all 3 cultures of material from the throat were negative for C. diphtheriae, and the patients did not receive antitoxin until pharyngitis became manifest. These cases demonstrate that in all probability autoinfection of the nasopharynx from the skin can occur.

In the other clinical cases the patients were admitted primarily for the pharyngitis or rhinitis, although in 5 of them the ulcers antedated the diphtheria of the throat for periods varying from three to seven weeks.

22. Dudley, S. F.: Critical Review: Schick's Test and Its Applications, Quart. J. Med. **22**:321-379, 1929.

Neuritic Complications.—Many patients with peripheral neuritis and pharyngeal and ocular palsy have been seen in military hospitals serving the Pacific area. Some of these have been associated with clinically recognized and bacteriologically confirmed nasopharyngeal diphtheria. Many writers, including Norris, Kern, Schenck and Silcox,[23] have commented on the great frequency of neuritis as a complication of diphtheria in the tropics, despite the mildness of nasopharyngitis. Perhaps it is the mildness which accounts for the apparently high incidence of neuritis; i. e., many cases are so mild that they are probably dismissed as cases of ordinary nasopharyngitis, unless routine cultures are taken. This has been our experience as

TABLE 9.—*Neurologic Complications in Patients Proved to Have Cutaneous Diphtheria*

Reference	Total No. of Patients with Ulcers	No. with Neurologic Complications	Nature of Complication: Paralysis of Accommodation	Nature of Complication: Paralysis of Pharynx	Nature of Complication: Peripheral Neuritis *	Comment
Cameron and Muir [6]	66	5 without C. diphtheriae elsewhere	..	..	5	
		7 with C. diphtheriae in skin and elsewhere	1	2	6	
Bensted [15]	31	3	..	..	3	One patient with lesion on face had facial neuritis
Walshe [5]	30 (selected group)	..	10	..	30	No report of culture of nose and throat
Fleck, Kellam and Klippen [9]	4	1	..	..	1	Patient also had myocarditis
Present report	174†	3	..	..	3	See table 10

* Peripheral neuritis includes sensory, motor and reflex manifestations.

† The follow-up data were incomplete for reasons explained in the text: (a) The 89 patients from the Saipan group (Twenty-Seventh Division) were not to the time of writing followed long enough for neuritis to occur; (b) the careful successive physical examinations necessary to detect minor signs of peripheral neuritis could not be performed even in the majority of the other instances for military reasons of transfer to other areas and for other reasons.

well as that of others.[9] The mildness of the nasopharyngeal disease in the face of the high incidence of neuritic complications is difficult to explain. The possibility that tropical strains of C. diphtheriae may be different from those of temperate climates should be investigated. A more likely explanation is based on Dudley's [20] theory of "latent immunization"—that owing to its widespread dissemination among troops in the tropics C. diphtheriae has raised the concentration of antitoxin in the blood of some persons to a level higher than that in

23. Norris, R. F.; Kern, R. A.; Schenck, H. P., and Silcox, L. E.: Diphtheria in the Tropics: A Report of Eighteen Cases on a United States Naval Hospital Ship, U. S. Nav. M. Bull. **42**:518-524, 1944.

the unexposed but not enough to reverse the Schick reaction or to prevent the absorption of toxin to an extent sufficient to result in neuritis. Only detailed correlated studies of serum levels of antitoxin can adequately put the latter hypothesis to the test.

Neuritis has also been noted in cases of cutaneous diphtheria originating in the tropics (table 9). Some of these [5] are particularly difficult to evaluate, since there is no record of an attempt to rule out the existence of C. diphtheriae in the nose and the throat. The material encountered by us can be subdivided as follows:

Group A: Neuritis complicating proved cutaneous diphtheria without evidence of C. diphtheriae elsewhere.

Group B: Neuritis associated with ulcers of the skin unhealed at the time of admission but not demonstrated to contain C. diphtheriae.

Group C: Neuritis in persons with scars of tropical ulcers.

Group D: Neuritis in persons with scars of tropical ulcers and history of sore throats.

Group E: Neuritis in persons proved to have diphtheritic pharyngitis.

Group F: Other cases of neuritis clinically indistinguishable from diphtheritic neuritis.

Group A: In table 10 are summarized the salient clinical features of the 3 patients in the present series in whose ulcers toxigenic C. diphtheriae was actually demonstrated. The patients are all derived from the group of 85 patients with ulcers seen in the Thirty-Ninth General Hospital. Most of those in the Saipan group were not observed for a sufficiently long period to the time of writing for neuritis to have developed. None of these men had a history of sore throats, nor did routine cultures of material from the nose and the throat yield these organisms. In these 3 patients the symptoms began between three and seven months after the lesion was first noted by the patient. In 2 of them the lesion occurred two and four months respectively after the time that the virulent C. diphtheriae was first isolated from the lesions. In pharyngeal diphtheria (group E) the neuritis most commonly begins within six weeks after onset.[24]

Unlike the nature of the complications following pharyngeal diphtheria, the cranial nerves were not involved in cases in which the lesions proved to be purely cutaneous. A glance at table 9 will show that this has been true also of previously reported series. Obviously, it is difficult to be certain in any instance that the organisms had never been present in the nose or the pharynx, but the clinical differences in the manifesta-

24. Cecil, R. L.: A Text-Book of Medicine, Philadelphia, W. B. Saunders Company, 1935.

TABLE 10.—*Neuritis in Patients with Tropical Ulcers*

Patient	Date of Onset and Healing of Ulcers	Date Admitted to Hospital and Lesions Observed	Result of Schick Test	Treatment	Apparent Date of Onset of Neuritis and Symptoms	Spinal Fluid Examination Results	Cultures of Material from Nose and Throat
				Group A			
Y21*	July 1943; healed 11/19/43; recurred 12/15/43; healed 2/14/44	10/10/43; multiple typical ulcers of buttocks and ankles	+ (10/31/43) — (1/3/44)	40,000 units D.A.T.‡ (11/1/43); saline soaks	2/20/44; numbness in feet; hypesthesia from ankles down; difficulty in standing on toes	Protein 105 mg. % (2/20/44); 125 mg. % (4/24/44)	Negative (10/28/44 and 11/16/44); later also negative
Y25	May 1943; healed 10/1/43	8/30/43; typical ulcers of feet	— (9/1/43)	20,000 units D.A.T. (9/6/43); saline soaks	10/20/43; numbness beginning in hands and then involving feet; "glove and sock" hypesthesia; hyporeflexia of right leg	Protein 68 mg. % (10/30/43)	Negative (9/1/43)
Y29	November 1942; healed ?; recurred July 1943; healed 11/20/43	10/9/43; typical ulcers of elbows, ankles, postcoccygeal region (fig. 10)	— (10/12/43)	Saline soaks; no D.A.T.	10/20/43; paresthesia in fingers and toes	Protein 68 mg. %; colloidal gold curve 5443333000 (10/25/43)	Negative (10/12/43 and 11/16/43)
				Group B			
M†	July 1943	9/2/43; typical ulcers of feet (fig. 11)	— (9/4/43)	No D.A.T.	9/10/43; paresis of accommodation	170 mg. % (11/17/43)	Negative (9/13/43)
B	September 1943; healed 12/18/43	11/18/43; typical ulcers of legs and feet	— (date not recorded)	No D.A.T.	12/27/43; numbness of feet; plantar hypesthesia; diminished deep reflexes	Pandy reaction 2+; colloidal gold curve 0000000000 (3/14/44)	None recorded
				Group C			
D	8/10/43; healed ?	1/4/44; scars of calves and toes	+ (1/5/44)	No D.A.T.	End of Sept. 1943; paresthesia and weakness of calves; hypesthesia and diminished vibration sense of legs; absent deep reflexes	Protein 85 mg. % (1/8/44)	Negative (1/5/44)
N	July 1943; healed September 1943	November 1943; scars on all four extremities and of buttocks	— (Nov. 1943)	No D.A.T.	One week after onset; numbness in fingers and toes ?; slight difficulty in swallowing; general weakness; hypesthesia of legs	Protein 39 mg. % (Nov. 1943)	Negative (Nov. 1943)
				Group D			
W	Sore throat 8/7/43; ulcers a few days later	10/7/43; scars on right hand, left finger and right leg	+ (10/8/43)	No D.A.T.	Sept. 5; transient difficulty in swallowing; Sept. 12; weakness and paresthesia; hypesthesia, "glove and sock"; deep reflexes of legs absent	Not examined	Negative (Oct. 1943)
Bj	Ulcers Feb. 1943; others and sore throat Sept. 1943; healed Nov. 1943	1/8/44; scars of legs and hands	— (1/9/44)	No D.A.T.	Late October; blurring of vision; end of Nov. 1943; numbness in extremities; muscular weakness; loss of deep reflexes; hypesthesia and loss of vibration and position sense	Protein 68 mg. % (1/17/44); 53 mg. % (2/22/44); colloidal gold curve 0000000000	None recorded
P	8/10/44; ulcers healed ?; indefinite history of occasional sore throats	12/29/43; scars of neck, arms and legs	— (1/15/44)	No D.A.T.	Late November; blurring of vision (transient); Jan.; weakness; hypesthesia; loss of proprioceptive sense and deep reflexes	Protein 81 mg. %; colloidal gold curve 0011100000 (1/19/44); 36 mg. % (3/10/44)	Negative (1/17/44)
S	May 1943; ulcerative dermatitis of heels; repeated sore throats and tonsillitis	12/6/43; scars of heel	Not recorded	No D.A.T.	12/3/43; hypesthesia distal parts of all extremities, thorax and abdomen	Protein 68 mg. % (12/11/43)	None recorded

* The patient was not discharged from hospital in the United States until October 1944.
† Patient had tachycardia. Changes in electrocardiogram (Sept. 11, 1943), gradually resolving by Dec. 30, 1943.
‡ D.A.T. is diphtheria antitoxin.

tions of the neuritis suggest that the pathogenesis of the lesion may actually be the production of toxin by the organisms in their cutaneous location.

The first symptoms of neuritis in the cases in which the lesions are purely cutaneous are usually those of paresthesia followed by weakness of the extremities. The observations on physical examination may be minimal and are usually those of hypesthesia to pinprick and light touch. The deep reflexes are usually diminished or totally absent. Position sense is altered in some instances.

Elevation of protein in the spinal fluid, as is to be expected in any form of neuritis, is present at some time in almost all these patients. It is a valuable observation in that it affords evidence that the patient is not malingering. In no instance has there been pleocytosis, although this condition has been recorded by some,[3] but occasionally changes in the colloidal gold curve occur (see patients Y29 and P in table 10). The long persistence of the elevation of the protein in the spinal fluid is demonstrated in some of these records.

Groups B, C and D: The symptoms, signs and laboratory observations are similar to those of group A, except that C. diphtheriae was not demonstrated. The long interval of time elapsing between the onset or even the healing of the lesion and the appearance of the neuritis has been noted by others.

Although the history of sore throat from some of the patients in group D is indefinite, this factor must be given great consideration despite the presence of the scars of the ulcers. It is notable that 2 of these patients had evidence of cranial nerve palsies.

Group E: There were 4 patients among the group of 34 patients with nasal or faucial diphtheria in the Thirty-Ninth General Hospital and 3 among the 37 patients from the Twenty-Seventh Division in whom neuritis developed during the six weeks of our observation. One of the former group (Y42) had diphtheritic ulcers of the skin as well as unilateral diphtheritic rhinitis at the time of admission.

In most instances the neuritis developed approximately six weeks after the onset of the sore throat. It is notable that 5 of the 7 patients had cranial nerve palsy manifested by difficulty in swallowing with regurgitation of the food through the nose. In 6 of the 7 there was peripheral neuritis of the same sort observed in the other groups. The spinal fluid of 2 patients was examined and showed total protein elevated to 58 mg. and 170 mg. per hundred cubic centimeters, respectively.

Group F: Shortly after the opening of the Thirty-Ninth General Hospital 6 patients with neuritis were transferred from a naval hospital. The records of these are no longer available. Their conditions were suspected to be of diphtheritic causation, but proof was lacking.

* The patient was not discharged from hospital in the United States until October 1944.
† Patient had tachycardia. Changes in electrocardiogram (Sept. 11, 1945), gradually resolving by Dec. 30, 1945.
‡ D.A.T. to diphtheria antitoxin.

Since the diphtheritic nature of certain tropical ulcers became apparent, there has not been an instance in which neuritis of the type discussed in the foregoing paragraphs could not be related to the ulcers, to sore throats or to proved diphtheritic pharyngitis or dermatitis.

Treatment.—After the diphtheritic nature of certain tropical ulcers was recognized, all ulcers at the time of the patient's admission to the hospital were treated as dangerous wounds. When C. diphtheriae was demonstrated, the patients were isolated. In handling outpatients, especially with regard to the Twenty-Seventh Division, a centrally located clinic was established to which all patients with ulcers were referred for cultures. Patients found to have C. diphtheriae were admitted to the hospital. In this way the patients were placed under treatment, and a curb was put on dissemination of the organisms.

Tables 11 and 12 summarize data concerning various factors in therapy. The most important principle in promoting healing of the ulcers seems, in our experience, to be rest in bed and the application of moist dressings. If the patients are treated as outpatients in the usual

TABLE 11.—*Relation of Toxigenicity of C. Diphtheriae to Healing Time in Hospital*

	Number of Patients	Mean G Healing Time, Days
Organisms toxigenic	107	19.2
Organisms atoxic	21	11.4

"Healing Time" does not refer to total days of hospitalization, nor does it refer to total time of existence of ulcer.
Mean G is the geometric mean.

fashion with a paste containing a sulfonamide compound and dry dressings, the lesions remain unhealed for many weeks and the patients continue to be a prolific source of diphtheria bacilli.

Ulcers containing atoxic organisms tend to heal more rapidly under hospital treatment (table 11) than those containing toxigenic organisms.

A relatively high level of antitoxin in the patient's blood as indicated by absence of reaction to the Schick test also seems to favor healing, although there are, as yet, insufficient data to prove this statement statistically. Serum therapy of chronic ulcers in persons with positive Schick reactions has not in our hands been productive of remarkable results, although some writers [25] have recommended the use of small doses of serum. Certainly serum is not lethal to the organisms, which may persist for many days after the treatment. One patient (Y43) had the organisms in the lesion five days after the intramuscular administration of 20,000 units. Antitoxin, however, acts as a prophylactic in preventing the serious consequences of autoinfection

25. Manson-Bahr, P.: The Prevalent Diseases of Libya, Lancet **1**:253-255, 1941. Bensted.[15] Cameron and Muir.[6] Craig.[4]

of the nose and the throat. After several examples of this had been observed, antitoxin was given to almost all the patients with positive Schick reactions. Antitoxin did not prevent the subsequent development of neuritis when given late, even during the course of a cutaneous infection (table 10, group A). That serum administered to patients with nasopharyngeal infection to prevent this complication is ineffectual when given after the third day has been stressed in Rolleston's [3] table.

When penicillin became available, observations were made to determine its effect. From a comparison of groups 1 and 7 in table 12, it seems that the actual healing time is shortened by two days at the most. Nevertheless, penicillin locally applied in concentrations of 250 units per cubic centimeter of saline solution gave certain definite indications of efficacy. This became evident during the course of a

TABLE 12.—*Lesions Containing Toxigenic C. Diphtheriae; Relation of Type of Treatment to Healing Time in Hospital*

Group Number	Treatment	Result of Schick Test	Mean Healing Time, Days	Number of Patients
1	Local *	—	18.6	27
2	Local	+	39.0	1
3	Antitoxin	—	43.3	3
4	Antitoxin	+	25.2	20
5	Antitoxin and penicillin	—	7.4	3
6	Antitoxin and penicillin	+	18.0	6
7	Penicillin	—	16.5	43
8	Penicillin	+	14.1	3

* Local treatment excluded penicillin applications.

series of controlled observations on patients who failed to react to the Schick test and whose lesions contained toxigenic bacilli. The lesions of 1 of these patients are illustrated by figures 12 and 13 and are described in the legend of figure 12. The lesions on the right leg, which were subjected to the local as well as the systemic effects of the penicillin, assumed a healthy granulating appearance sooner than the others. In them, although they were larger and had more adherent necrotic material than the others, C. diphtheriae had disappeared after forty-eight hours of treatment, whereas in one of those on the left leg the organisms persisted until the fifth day. Under the influence of penicillin locally applied the bacterial flora gradually changed after the second day so that gram-negative bacilli, especially Bacillus pyocyaneus and Alcaligenes faecalis, came to replace the gram-positive bacilli and cocci which predominated at first. In a series of 5 patients from the Saipan group (S5, S27, S36, S44 and S54) penicillin was not given intramuscularly, but in each instance an ulcer treated locally with penicillin was compared with a control treated with saline solution. In each case the Klebs-Löffler bacilli had disappeared from the lesions forty-eight hours after the application of penicillin, whereas the organ-

Fig. 12 (patient Y56).—Multiple diphtheritic ulcers of lower extremities. The patient was given 300,000 units of penicillin a day intramuscularly in five doses for eight days. The right leg also received compresses of isotonic solution of sodium chloride containing penicillin (250 units per cubic centimeter) for four hours in the morning and four hours in the afternoon. Soaks of isotonic solution of sodium chloride were applied to the left leg for control at all times and to the right leg in the intervals between the applications of penicillin. The patient showed no reaction to the Schick test at the time of his admission.

A, right leg, May 24, 1944, at the start of treatment.

B, left leg, May 24. *C* and *D*, right leg, May 27, after three days of penicillin locally. *E*, left leg, May 27—control. *F* and *G*, right leg, May 31, after seven days of penicillin. *H*, left leg, May 31—control.

Fig. 13 (patient Y56).—*A* and *B*, right leg, June 10, 1944, after seventeen days of local penicillin therapy.

C, left leg, June 10. Penicillin had been applied as in the case of the right leg, beginning June 6.

D and *E*, general view, comparable to *A* and *B* of figure 12, June 26. The lesions are almost healed.

F, *G* and *H*, close-ups, comparable to *C*, *D* and *E* of figure 12, June 26. Note the development of bronze pigmentation.

isms were at that time still present in the ulcers treated with the simple pack of saline solution. Gram-negative flora was again predominant where the exudate had been in contact with the penicillin. An examination of 1 patient with a positive Schick reaction (Y57; fig. 14) showed a similar disappearance of C. diphtheriae within forty-eight hours and a like change in the flora.

The removal of C. diphtheriae is obviously desirable both in reducing the danger of neuritis and in lessening the epidemiologic hazard. Further information is necessary concerning this point. It is

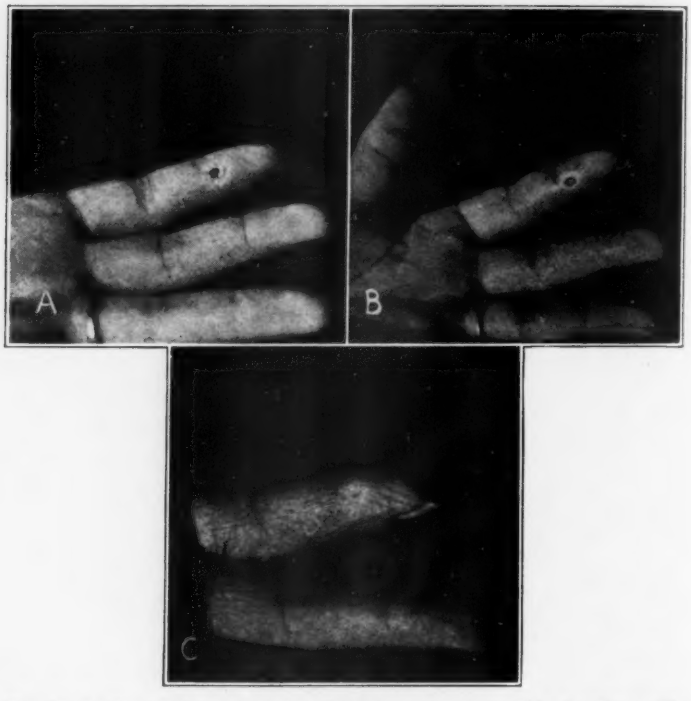

Fig. 14 (patient Y57).—*A*, diphtheritic ulcer of one month's duration. There was no history of injury. The patient had a positive Schick reaction.

B, after six days of treatment with penicillin.

C, after nineteen days of treatment with penicillin.

important also to culture material from the nose and the throat before the patient is released from isolation.

Although C. diphtheriae is sensitive to sulfonamide compounds in vitro, it seems to be almost unaffected by these drugs when present in the ulcers. In many instances the organisms were isolated directly from lesions packed with crystals or covered with ointments containing

sulfonamide compounds. This is confirmed clinically by the fact that many of these same outpatients had been thus treated for months before the cultures were made, with slow, if any, improvement or occasional progression, of the lesions. Applications of sulfonamide compounds give the lesions a cleaner appearance.

In a few cases special measures have been taken. Among these is the application of casts to secure immobilization where this has been difficult to obtain by other means. Excision of the lesion has been practiced in one very unresponsive ulcer, with primary healing of the wound. This may shorten the period of hospitalization in particular instances. Skin grafts have been applied to the bases of some large ulcers after they began to granulate cleanly, but these grafts usually fail to take.

EPIDEMIOLOGIC SIGNIFICANCE OF CUTANEOUS DIPHTHERIA

Evidence Gathered from Contacts in Thirty-Ninth General Hospital.—Considerable evidence has accrued that cutaneous diphtheria, particularly when unrecognized, is important in spreading the bacilli not only to the skins but also to the noses and the throats of others. This was most clearly demonstrated when infection apparently the result of contact developed in 7 persons in the Thirty-Ninth General Hospital, 6 among ward personnel and 1 among the patients, before tropical ulcers were recognized to be diphtheritic. A nurse caring for an officer (patient Y68) with widespread desquamative and ulcerative lesions, resembling those in patient Y65 (fig. 6), had a paronychia and an abscess in her arm from which C. diphtheriae and beta hemolytic streptococci were isolated. Another nurse caring for the same patient had a sore throat, which was not of the membranous type. This nurse was known to have been negative to the Schick test two years previously. C. diphtheriae was isolated from her throat. In another officer, who was admitted for jaundice two weeks previously and who did not have a sore throat at the time of admission, in the cubicle next to that of patient Y68, there developed extensive membranous nasal and pharyngeal diphtheria. In a wardman (Y20, fig. 7 *B*) in another ward, where many patients with tropical ulcers were kept, there developed a paronychial granulomatous and ulcerative lesion from which the toxigenic corynebacteria were isolated, and shortly thereafter another attendant in the same ward had diphtheritic pharyngitis. A wardman working in another ward for patients with cutaneous diseases, where there were many patients with ulcers, contracted pharyngeal diphtheria.

After the patients with the ulcers were isolated until they proved to be nondiphtheritic, there were no further cases of infection developing as a result of contact except 1 in which a nurse, attendant on an isolated patient with diphtheritic pharyngitis, contracted severe membranous

nasal diphtheria. From all 8 of these patients infected by contact virulent corynebacteria were isolated.

Direct evidence of autoinfection of the pharynx in persons harboring the organisms in the skin is presented in the section entitled "Associated Clinical Observations."

In all reported outbreaks of diphtheritic tropical ulcers among military populations the incidence of ulcers (table 1) has exceeded that of nasopharyngeal diphtheria and carriers. Furthermore, the carrier rate among persons without ulcers may be low. In a study of the carrier rate among 201 men of the Thirty-Fifth Infantry in the Twenty-Fifth Division, only 2 carriers, both with nasal infections and without symptoms, were discovered. Likewise, in the Twenty-Seventh Division,

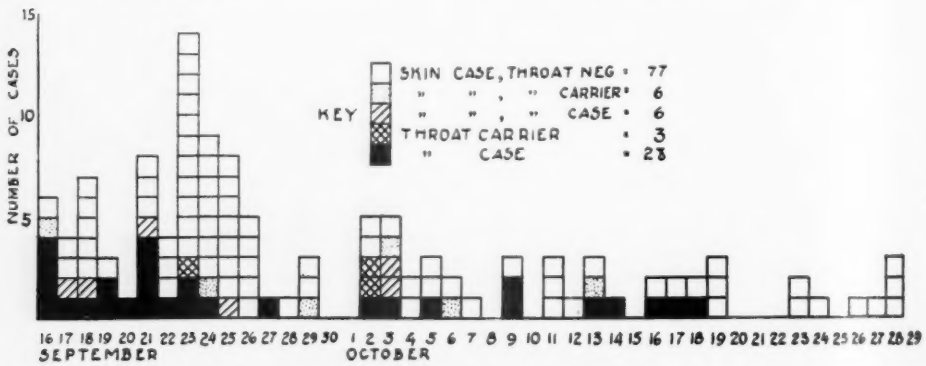

Fig. 15.—Cases of diphtheria in the Twenty-Seventh Division in a rest area. Each block represents 1 case. The date of the patient's admission determines the position of the block, unlike figure 2 in which the date of onset is charted. The relative infrequency of the cases of extracutaneous diphtheria toward the right of the figure is obvious.

routine study of approximately 600 men resulted in the discovery of only 3 pharyngeal carriers who did not have ulcers of the skin. The total incidence among these 801 then is 0.6 per cent. Among patients with diphtheritic ulcers, however, 7 asymptomatic carriers were discovered in the entire series of 174 patients, an incidence of 4 per cent.

As the patients with ulcers were removed from the division in the rest area, the incidence of nasopharyngeal diphtheritic infection decreased rapidly. The experience in the case of the Twenty-Seventh Division is illustrated in figure 15. It is similar to that with the Twenty-Fifth and Forty-Third Divisions and almost identical with that of Bensted [15] and his troops in Northern India (see his chart).

Possible Relation to Outbreak of Diphtheria in Europe.—Certain correlations suggest that the skin may be the ultimate source of bacilli affecting much larger susceptible populations. During the World War II

there has been a remarkable increase of diphtheria in Europe (fig. 16). It is of great note that this coincided with the beginning of the return of German soldiers of the African Corps to Europe. In this connection the considerable outbreaks of diphtheria among German prisoners

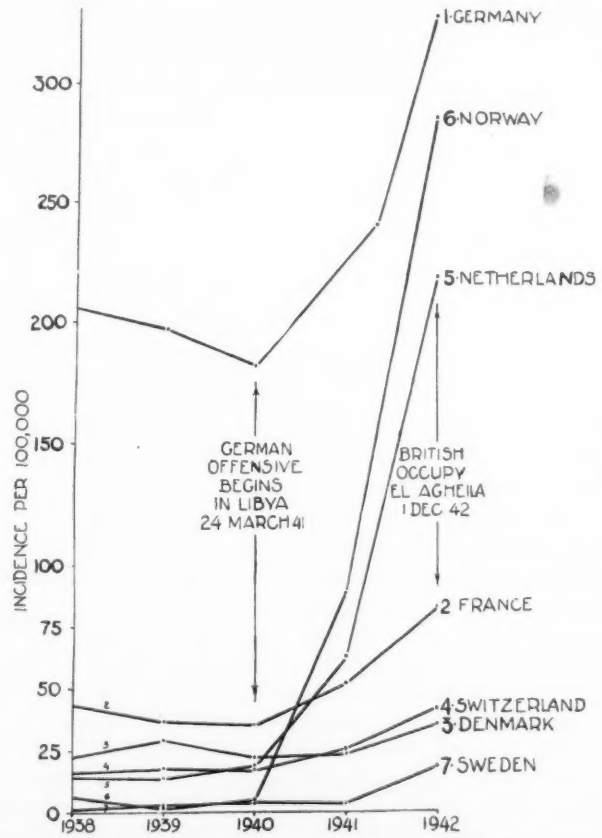

Fig. 16.—Rate of occurrence of diphtheria in European countries from 1938 to 1942, inclusive. The information on which this chart is based was obtained from the data contained in "Diphtheria Susceptibility and Immunization," Bull. U. S. Army M. Dept., 1944, no. 76, pp. 104-108, and in the War Department Technical Bulletins. The statistics of population on which the incidence per hundred thousand is estimated are those contained in "The World Almanac" for 1944.

Incomplete figures for 1943 indicate a continued enormous rise in the incidence in Norway and the Netherlands to more than double that of 1942 in each country.

of war captured in Africa and confined in camps in the United States and Trinidad, British West Indies, must be mentioned. The description of an outbreak in such a camp [9] is particularly interesting, since

4 of the ulcers, which were said to be numerous, were proved to be diphtheritic. Among Italian prisoners of war, however, there have been no epidemics as far as is known to the writers.

The rise in diphtheria rates during 1941 was most striking in Norway, a country with a previously very low diphtheria rate and where immunization had not been practiced. It may be presumed that German troops were sent to rest in relatively pleasant and inactive areas, such as Norway and the Netherlands. Certainly in the former country the German conqueror was relatively scrupulous; dietary condi-

TABLE 13.—*Incidence of Toxigenic and Nontoxigenic Strains of C. Diphtheriae in Patients with Extracutaneous Diphtheria and in Carriers*
(Thirty-Ninth General Hospital, Feb. 7, 1943 to July 1, 1944)

	Patients			Carriers				
C. diphtheriae toxigenic (total, 39).	Throat	Nose and Throat	Nose	Throat	Nose and Throat	Nose	Nose and Sputum	Nose and Ears
No ulcers.....	23	1	3	2	2	1	..	..
Cutaneous diphtheria also present	4	..	2	..	..	1	..	..
C. diphtheriae atoxic (total,10).....	1	..	..	2	1	4	1	1
Total.....	28	1	5	4	3	6	1	1

Grand total of patients and carriers, 49

tions were relatively good, and there was no necessity for frequent unnatural crowding, as in shelters, to amplify the epidemiogenic opportunities of the Klebs-Löffler bacilli. It is interesting to note that the two neutral countries, Switzerland and Sweden, showed a delayed and slight rise. Recent information indicates that the increase in morbidity from diphtheria in France was largely in the occupied zone. The very slight increase in Austria is difficult to understand, unless this country was out of the line of evacuation from the desert.

In New Zealand—to consider a country remote from the war and well fed—a rise in diphtheria morbidity began in 1942 and continued through 1943 as follows: 1940, 368; 1941, 383; 1942, 642; 1943, 830. Perhaps an explanation is the increment in the concentration of the etiologic agent supplied by marines and soldiers returning from the area of the Solomon Islands.

The diphtheria in the former, whose influx into the country began in 1942, is described by Norris, Kern, Schenck and Silcox.[23] The Twenty-Fifth Division appeared en masse in New Zealand in 1943. Thus the stream of persons infected with C. diphtheriae has been uninterrupted until the middle of 1944. The drafts of New Zealand soldiers from Africa did not return to New Zealand until the middle of July 1943, and they were not numerous. The previous peak in New

Zealand was in 1917 and 1918 and may have been associated with the return of soldiers at that time from Gallipoli, Turkey, and the desert.

It is of great interest that in the words of Friederich Löffler,[26] "the disease appears to have been perfectly well known in Egypt, Syria and Palestine even in ancient times. This is proved by repeated references to it in the Babylonian Talmud." Also, according to Rolleston,[3] in the first century A. D. "an unmistakable description of diphtheria is given by Aretaeus of Cappadocia under the name of Syriac or Egyptian ulcers owing to its having originated in Syria and Egypt whence it spread to all European countries." The term "ulcers" refers to the appearance of the throat and not to the skin in this instance.

These correlations are not held up as final proof but are presented for closer analysis when more detailed information becomes available, especially concerning the movements of German soldiers returned from Africa and the Middle East. From the evidence at hand, correlating the intimate observations made within the confines of a hospital concerning the epidemiologic significance of the diphtheritic skin with the larger facts of the concomitance of the cutaneous and pharyngeal forms among troops in widely scattered tropical and desert regions, and the increase in diphtheria in the countries of Europe, the problem assumes significant proportions. As Rolleston says, "subjects of clandestine diphtheria, like clandestine prostitutes, are of considerable epidemiological importance, as both, owing to their innocent appearance, may widely spread disease before their true nature is recognized.". Certainly the diphtheritic nature of "tropical ulcers" has not been widely recognized, and their frequently inconsequential appearance has made them particularly dangerous.

GENERAL CONSIDERATION OF DIPHTHERIA IN THE TROPICS

The Native Reservoir.—It is paradoxic that although clinical nasopharyngeal diphtheria is apparently rare among natives there is abundant evidence of the widespread dissemination of C. diphtheriae in the tropics in direct contrast to what has been observed in the coldest parts of the world.[27] The rarity of nasopharyngeal diphtheria and neuritis was attested by Captain Rutter, British medical officer in the Solomon Islands, Dr. Guépin of the French Colonial Medical Service in Espiritu Santo, New Hebrides, and the Fijian medical practitioner, Asari. Natives of low latitudes generally possess a high degree of immunity as evidenced by absence of reactivity when

26. Nuttall, G. H. F., and Graham-Smith, G. S.: The Bacteriology of Diphtheria, London, Cambridge University Press, 1908.

27. Heinbecker, P., and Irvine-Jones, E. I. M.: Susceptibility of Eskimos to the Common Cold and a Study of Their Natural Immunity to Diphtheria, Scarlet Fever and Bacterial Filtrates, J. Immunol. **15**:395-406, 1928.

given the Schick test. This has been found true of the Filipinos, Malays, Javanese, Hondurans and Brazilians. Among the Bantu of Africa [28] the incidence of Schick test immunity increases with age but more rapidly than among Europeans. This problem has recently been made the subject of an extensive study by Murray,[29] who compared the Schick test results, the carrier rates and the incidence of clinical diphtheria of rural and urban Bantu natives of Africa. In the 6 to 8 year (inclusive) age group the percentages of persons with positive Schick reactions were 11.8 for the rural and 17.2 for the urban children, and the respective percentages for the 15 to 17 year age group were 5.1 and 12.0. The percentages for white children in South Africa were approximately five times as high as those of the rural Bantu in the various age groups. Clinical diphtheria was rarely encountered under rural conditions but was commoner in the urban

TABLE 14.—*Schick Reactions of Solomon Islanders (Adult Males)*

	Natives of			
	Guadalcanal	Malaita	Florida	Total
Number tested	52	122	22	196
Number with positive reactions	2	9	0	11
Number with no reactions	50	113	22	185
Percentage with positive reactions	4	7.3	0	5.6

natives, and 53 per cent of the patients were in the age group of up to 5 years. The carrier rate for toxigenic C. diphtheriae was 3.2 per cent in the rural children and 1.8 per cent in the urban children, with toxigenic : nontoxigenic ratios of 1 : 1.1 and 1 : 2.5, respectively. It is interesting to note that approximately 4 per cent of the natives of India have been found to carry C. diphtheriae, and a similar carrier rate was found in the native children of Singapore (Hunter [30]). Murray did not consider that the cutaneous lesions which occur among the Bantu might be diphtheritic, and data were not presented concerning the Schick reactions in children less than 3 years of age.

During our military assignments the opportunity was given to investigate this paradox of high immunity so early in life, associated with relatively little obvious clinical diphtheria, and in particular to determine what role the skin might play. In an early experience, adult native Solomon Islanders were only rarely found to react to a

28. Grasset, E.: Studies on the Nature of Antidiphtheritic Immunity Among South African Bantu by Means of Schick Test and Antitoxin Titrations, South African M. J. **7**:779-785, 1933; cited by Dudley.[22]

29. Murray, J. F.: Diphtheria Amongst the Bantu, J. Hyg. **43**:159-169, 1943.

30. Hunter, P. S.: Annual Report for 1930, Health Department of Singapore, 1931; cited by Dudley.[22]

Schick test (table 14). Likewise in the New Hebrides, Tonkinese children over the age of 3 years were found usually to be negative to the Schick test (table 15). These children all lived in intimate personal contact with one another in a communal nursery under appalling conditions of dirt and were part of the same epidemiologic group as the Melanesian children living on the same plantation. Similar studies were later performed in the Marianas on Chamorros (table 16). Only between the ages of 7 months and 3 years was there any considerable proportion of persons with positive Schick reactions among the

TABLE 15.—*Schick Reactions of Tonkinese Children (New Hebrides)*

	Natives of Given Age				
	Up to 6 Mo.	7 Mo. to 1 Yr., Inclusive	13 Mo. to 3 Yr., Inclusive	More than 3 Yr.	Total
Number tested	3	10	28	12	53
Number with positive reactions	0	5	3	0	8
Number with no reactions	3	5	25	12	45

TABLE 16.—*Schick Reactions of Chamorro Children (Marianas)*

	Natives of Given Age				
	Up to 6 Mo.	7 Mo. to 1 Yr., Inclusive	13 Mo. to 3 Yr., Inclusive	More than 3 Yr.	Total
Number tested	7	13	23	45	88
Number with positive reactions	0	9	15	2	26
Number with no reactions	7	4	8	43	62

Tonkinese and Chamorro children (67 per cent in the case of the letter). Persons more than 3 years of age with positive Schick reactions were rare.

It seemed logical to seek other than the racial factors considered by some [29] as an explanation of this phenomenon. The racial element seemed unlikely, since members of diverse races, e. g., Solomon Islanders, Bantu Africans, Tonkinese and Chamorros, exhibited the same phenomenon and since if young enough children were investigated a sharp peak in the curve of positive reactions became apparent. On the other hand, these native people have in common a tropical environment, intimate personal contact and the unwashed state, all of which favor the existence of cutaneous diphtheria. The factor operative early in life to reverse the loss of transplacentally acquired immunity so rapidly was therefore sought in the skin.

The existence of a large cutaneous reservoir of diphtheria became apparent when the skins of the children were examined. Two of 4

Melanesian natives with deep, punched-out ulcers (fig. 17), one of them apparently superinfected yaws, yielded nontoxigenic C. diphtheriae. Incidentally, one foul-smelling phagedenic lesion in an adult black New Hebridean was found to contain spirochetes and fusiform bacilli as described by James.[2] Six of the 53 Tonkinese children had multiple punched-out ulcerative lesions of the skin which resembled the tropical ulcers observed in our soldiers but which were generally more superficial (fig. 18). Four of these yielded organisms with the morphologic and fermentative characteristics of C. diphtheriae mitis but which were not toxigenic. Lesions of identical appearance were found in large numbers among the Chamorro children. Fifteen strains of C. diphtheriae

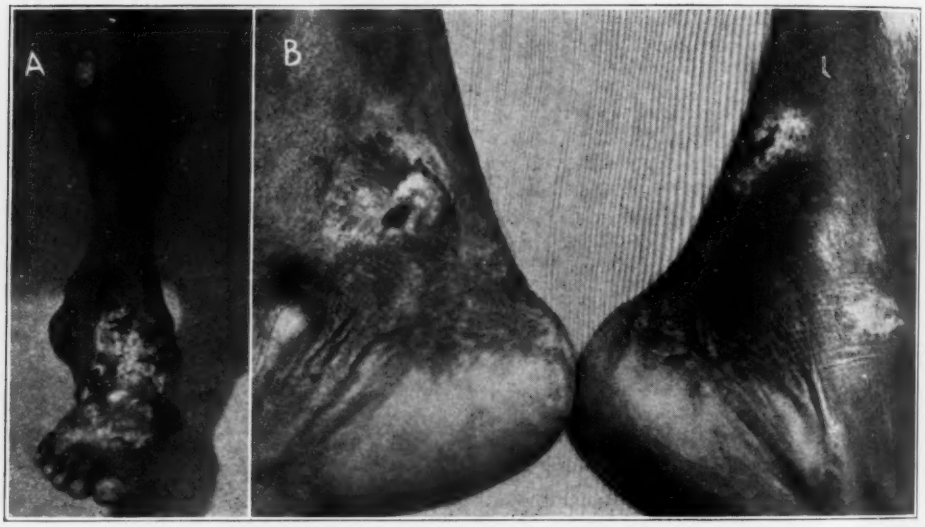

Fig. 17.—*A* (patient TN32), yaws of the right foot with punched-out ulcerations observed in a Melanesian child of the New Hebrides. A typical "ecthymatous" ulcer of the skin is also shown. The ulcerative lesions in both instances contained nontoxigenic C. diphtheriae.

B (patient TN4), chronic ulcers of ankles containing C. diphtheriae (nontoxigenic) observed in a Melanesian native of Espiritu Santo.

mitis were tested for toxigenicity, and one of these was found to be toxigenic. It is interesting to note and not easy to explain that some of these open lesions occurred in older children who showed no reaction to the Schick test. They were most numerous in areas where trauma was most likely to occur, as about the knees, but they also occurred elsewhere. Their appearance at various stages is shown in figure 18. These scars were absent in children less than 7 months of age and were almost universal in those above the age of 3 years. They were

much less numerous among the persons with positive Schick reactions. Studies of 14 Melanesian natives and 12 Tonkinese revealed that they were not nose and throat carriers. In the Marianas, however, 2 of 18 natives were found to harbor C. diphtheriae in the nasopharynx.

All these observations indicate that an enormous reservoir of C. diphtheriae exists in tropical and hot desert regions, probably throughout the world, and that the damp skin in closely associated and unwashed

Fig. 18 (patient TN38).—Multiple ulcers in a Tonkinese child, aged approximately 2 years. Some have a punched-out appearance. Some are partly or completely scarred, with bronze-violaceous pigmentation of the surrounding skin. Atoxic C. diphtheriae was observed in a culture of material from one of the ulcers.

herds may be the source as well as the immunizing agency. The barrier of cleanliness accounts for the fact that white people living in the tropics are always more susceptible than the natives, as indicated by the results of the Schick test, and that the former often have clinical nasopharyngeal diphtheria, sometimes in epidemics. One such epidemic

was observed by Fox and MacDonald (cited by Forbes [31]) in a school at Shillong in Assam, India, that very region where tropical ulcers have been so common in the natives as well as among the Allied Forces.

In a tropical country such as Formosa, where there is a reservoir group analogous in environment to that of the Tonkinese in the New Hebrides, as well as a relatively well-to-do and clean group, nasopharyngeal diphtheria may become the commonest disease of bacterial causation.[32]

Among troops under conditions of combat in the tropics the situation becomes entirely analogous to that of the natives in their usual state. First, the skin is both warm and moist so that nasopharyngeal flora find conditions in the integument similar to those in the pharynx. Even in temperate zones nurses and others in contact with diphtheritic patients have been found to harbor this organism in the skin, e. g., under the finger nails. There is, moreover, often intimate contact with others in foxholes which often are of a three man or communal type. Under some circumstances, as in the Marianas, there was also frequent contact with the native population. Furthermore, during combat numerous minor traumas occur. The important difference between the native and military groups is that in the adult soldiers there is a much higher proportion of persons susceptible to diphtheria. Thus, C. diphtheriae, once established, spreads readily not only from skin to skin but also from skin to nasopharynx and in the reverse direction. Direct evidence of the pharyngeal source of an extrapharyngeal infection is the case of diphtheria of the penis illustrated in figure 9 *A*.

The original source of the C. diphtheriae is difficult to determine. Carriers are always present in our own military population [33] and the native reservoir may at times be important.

SUMMARY AND CONCLUSION

Tropical ulcers of the deep, punched-out type occurring in soldiers under combat conditions in the South and Central Pacific areas often contain toxigenic C. diphtheriae, particularly when cultured within six weeks of onset.

A simple but careful technic is necessary to cultivate the organisms. Blood agar plates of slightly alkaline reaction, prepared so as to avoid

31. Forbes, J. G.: The Prevention of Diphtheria, Medical Research Council, Special Report Series, no. 115, London, His Majesty's Stationery Office, 1927.

32. Epidemiology of Diseases of Naval Importance in Formosa, United States Navy Department, Bureau of Medicine and Surgery, 1944.

33. Meehan, J. W., and Michie, H. C.: Diphtheria, in Ireland, M. W.: The Medical Department of the United States Army in the World War, Washington, D. C., Government Printing Office, 1928, vol. 9, chap. 6, p. 233.

hemolysis and streaked in a manner to assure well isolated colonies, are most satisfactory for obtaining rapid and easily recognizable cultures.

The ulcers are disabling in themselves when they occur on the extremities, as they do most commonly.

Neuritis is an occasional complication of apparently purely cutaneous diphtheria, in which case the cranial nerves are rarely, if ever, involved.

Diphtheria should be considered the most probable cause of neuritis, even in persons found to have positive Schick reactions, among troops evacuated from tropical regions, particularly North Africa, India, Burma and the islands of the Pacific.

Evidence gathered from controlled experiments indicates that penicillin locally applied in isotonic solution of sodium chloride to the lesions, with the patient resting in bed, is the treatment of choice at present.

The fact that more persons with positive Schick reactions will be found among any group who have diphtheritic ulcers than among the general population suggests that the state in which no reaction can be elicited by the Schick test is at least to some extent protective against the development of tropical ulcers.

Diphtheria of the skin can result in autoinfection of the nasopharynx in persons with positive Schick reactions, and it also has epidemiologic importance, especially since the cutaneous form has often not been recognized. It may spread from skin to skin, as seems usually to be the case, or from skin to pharynx or the reverse. This was demonstrated in tracing contact infections in a hospital and in observing the course of outbreaks in three military divisions in which cutaneous and nasopharyngeal diphtheria were concomitant. The possibility is suggested, after one reviews recent trends in the incidence of diphtheria, that troops returning immediately from tropical and desert regions may be a hazard to large masses of susceptible civilians.

The existence of a tremendous cutaneous reservoir of diphtheria in natives of the tropics is demonstrated. The presence of C. diphtheriae in the skin accounts for the gradual immunizing of these people so early in life.

The factors that conspire to make cutaneous diphtheria relatively so important in the tropics are (1) the warm, moist condition of the skin, (2) the intimate association of the herd and (3) the unwashed state. When susceptible populations, such as white soldiers, are forced by the vicissitudes of combat into the same conditions, then severe faucial as well as the commoner cutaneous forms of diphtheria become widespread.

METHEMOGLOBINEMIA

Treatment with Ascorbic Acid

LIEUTENANT MILLARD CARNRICK
MEDICAL CORPS, ARMY OF THE UNITED STATES
B. D. POLIS
Senior Biochemist, Division of Laboratories, Philadelphia General Hospital
AND
THOMAS KLEIN, M.D.
Visiting Physician, Department of Medicine, Philadelphia General Hospital
PHILADELPHIA

CYANOSIS is caused most frequently by cardiac or pulmonary disease, but it may be the result of an increased concentration of methemoglobin, among other etiologic factors. In the absence of cardiac or pulmonary disease further study of the blood to establish or exclude the presence of this hemoglobin derivative is of considerable importance. We have recently encountered 2 patients presenting cyanosis as an important symptom. In 1 the disease is of unusual interest in that a spontaneous formation of methemoglobin was apparently the cause of the cyanosis. A similar syndrome was described by Stokvis in 1902 and named enterogenous cyanosis.[1] Since that time a few additional reports of spontaneously occurring methemoglobinemia in the absence of drug therapy have been described.[2] Unfortunately, laboratory examinations of the blood pigments were not always made. In the other patient sodium nitrite therapy was the cause of the cyanosis.

Methemoglobinemia is commonly accompanied not only with cyanosis but also with disturbances in gastrointestinal function; frequently diarrhea, usually of long duration, has been noted. In 1 of our patients the combination of cyanosis and gastrointestinal symptoms was prominent. In both patients methemoglobinemia was suspected and confirmed by laboratory studies.

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1. Stokvis, B. J.: Casuistic Contributions to the Autotoxic Enterogenous Cyanosis, Nederl. tijdschr. v. geneesk. **2**:678, 1902.

2. (*a*) Talma, S.: Intraglobuläre Methaemoglobinaemie bei den Mensch, translated, Berl. klin. Wchnschr. **39**:865, 1902. (*b*) Berron, G. A.: Enterogenous Cyanosis (Stokvis Syndrome), Rev. méd. Yucatan **13**:15, 1924. (*c*) Innes, F. R.: Case of Enterogenous Cyanosis, Indian M. Gaz. **66**:262, 1931. (*d*) Dunaevskiy, M. I., and Kozlovskaya: A Case of Autotoxic Methemoglobinemia, Vrach. delo **22**:367, 1940. (*e*) Traxler, P. S.: Methemoglobinaemia or Enterogenous Cyanosis, M. Bull. Vet. Admin. **20**:227, 1943. (*f*) King, E. J.; Gilchrist, M., and White, J. C.: A Case of Methemoglobinemia, Biochem. J. **38**:8, 1944.

Of particular importance in both cases was the striking response of the cyanosis to treatment with ascorbic acid, with concomitant alleviation of all clinical symptoms. We were not aware that ascorbic acid had been previously used at the time it was employed in the treatment of our first patient; however, perusal of the literature has since revealed that Lian and associates [3] were the first to use ascorbic acid in the treatment of methemoglobinemia. Subsequently other reports appeared.[4] Descriptions of the clinical observations in our patients and of their response to treatment with ascorbic acid follow:

CASE 1.—M. K., a 54 year old obese white woman, was admitted to the surgical service of Dr. William Erb in the Philadelphia General Hospital on July 8, 1944, because of a pain of six hours' duration in the right lower abdominal quadrant. From 1940 to 1943, during which time friends began to notice a change in the color of her skin, the patient had been taking silver nitrate pills for a "stomach ulcer." The patient took a teaspoonful of a saline cathartic a day for five or six months preceding admission, until she began to feel "sick to her stomach." A week before admission transient nonradiating pain in the right upper abdominal quadrant developed, which she stated was treated with mild mercurous chloride by her physician. This pain became generalized on the day before admission, and it was associated with several loose, watery, greenish stools. On the day of admission the patient was vomiting.

Physical examination on admission showed a temperature (oral) of 100 F., pulse rate 100 beats per minute and respiration rate 28 per minute. The patient, who on gross examination was retching and appeared acutely ill, was well developed and well nourished. The skin and mucous membranes showed the characteristic changes of argyria. The blood pressure was 130 systolic and 80 diastolic, but examination of the heart revealed no other abnormalities. The lungs were normal to auscultation and percussion. The abdomen showed poorly localized tenderness throughout but was soft, and peristalsis was normal.

Laboratory Examination.—Laboratory studies showed hemoglobin content 14 Gm. per hundred cubic centimeters and leukocytes 7,800 per cubic millimeter, with a normal differential count. The serum protein level was 6.9 Gm. per hundred cubic centimeters and chlorides as sodium chloride 584 mg. Sugar, urea and carbon dioxide-combining power were normal. The reaction to the Kline test was negative. On July 10 the icterus index was 22, but by July 19 it had fallen to 5. The serum cholesterol level was 272 mg. per hundred cubic centimeters, of which 159 mg. was esterified. Roentgenologic examination of the gallbladder showed poor function, but no stones or gross abnormalities were visible.

On admission a tentative diagnosis of acute cholecystitis was made. The patient was treated with morphine, atropine, 1/100 grain (0.6 mg.) of glyceryl

3. Lian, C.; Frumusan, P., and Sassier: Méthémoglobinémie congénitale et familiale: action favorable de l'acid ascorbique, Bull. et mém. Soc. méd. d. hôp. de Paris **55**:1194, 1939.

4. (*a*) Denny, J.; Murdock, E. T., and Rogan, J. J.: Familial Idiopathic Methemoglobinemia with a Note on the Treatment of Two Cases with Ascorbic Acid, Brit. M. J. **1**:721, 1943. (*b*) Graybiel, A.; Lilienthal, J. L., and Riley, R.: The Report of a Case of Idiopathic Congenital (and Probably Familial) Methemoglobinemia, Bull. Johns Hopkins Hosp. **76**:155, 1945. (*c*) King, Gilchrist and White.[2f]

trinitrate and fluids intravenously administered. The temperature became normal in six hours, but the patient still complained of pain in the abdomen and continued to vomit. It was noticed that, although the argyria was prominent, the nail beds appeared cyanotic; the diagnosis of enterogenous cyanosis was suggested. On July 10 a specimen of blood was examined spectroscopically and showed the presence of 3.6 Gm. of methemoglobin.[5] The plasma ascorbic acid level was 0.2 mg. per hundred cubic centimeters. Ascorbic acid therapy was instituted; the patient was given 500 mg. daily by mouth in divided doses for three days. There was noticeable improvement in symptoms within twenty-four hours. By the end of forty-eight hours the patient was able to tolerate food without pain

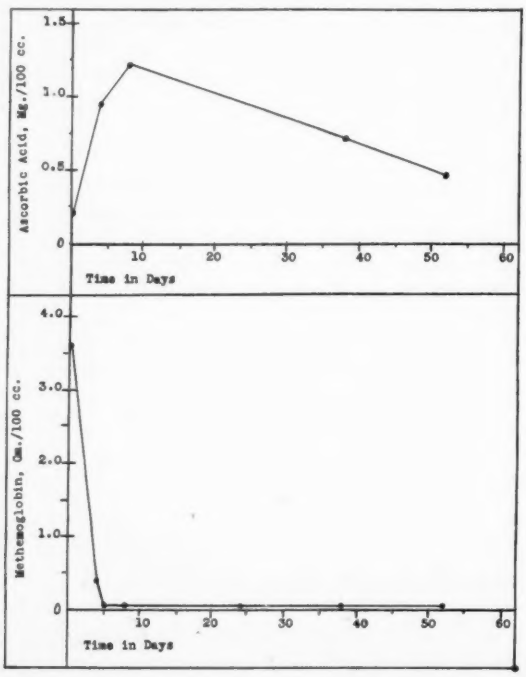

Chart 1 (case 1).—The upper curve portrays the ascorbic acid level of the blood after oral administration of a total of 4,500 mg. in the first six days of treatment. The lower curve illustrates the reduction in the methemoglobin content of the blood concomitant with the administration of ascorbic acid.

or vomiting. In seventy-two hours the methemoglobin level was merely a trace and the ascorbic acid level was 0.95 mg. per hundred cubic centimeters. The patient was then given 1,000 mg. of ascorbic acid daily. On July 15, five days after beginning therapy, there was no methemoglobin demonstrable in the blood. Since

5. Methemoglobin was determined spectroscopically by the procedure of Austin and Drabkin (Austin, J. H., and Drabkin, D. I.: Spectrophotometry of Methemoglobin, J. Biol. Chem. **112**:67, 1935) with a Bausch and Lomb visual spectrophotometer.

the patient was symptom free, she was discharged on July 26 and placed on a fat-free diet, with the diagnoses of acute cholecystitis, argyria and methemoglobinemia. Follow-up studies at monthly intervals have shown no return of the methemoglobin nor complaints referable to the gastrointestinal tract. An attempt was made to place the patient on a low ascorbic acid diet to reproduce the syndrome, but the patient was uncooperative.

CASE 2.—A. R., a 69 year old white woman, was admitted to the ophthalmologic ward of the Philadelphia General Hospital, service of Dr. Diechler, because of severe pain and a loss of vision in the right eye of three weeks' duration and a loss of vision in the left eye of thirty-six hours. The patient complained of

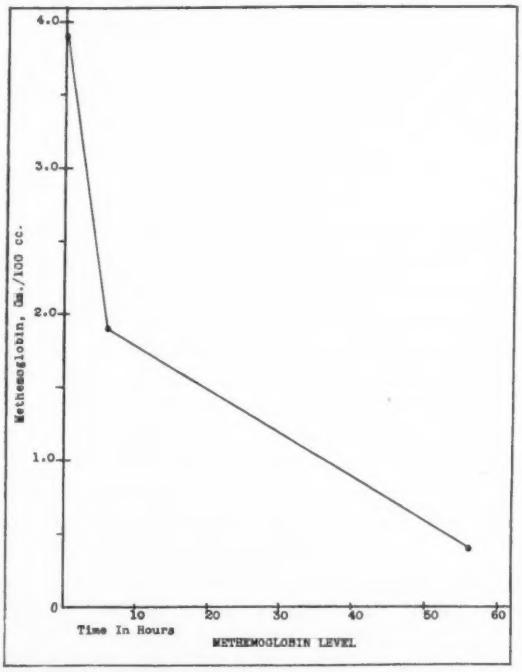

Chart 2 (case 2).—Methemoglobin level of the blood after intravenous administration of a total of 1,000 mg. of ascorbic acid in the first nine hours of treatment. No additional ascorbic acid was administered after the initial nine hour period.

rings around lights, loss of vision and vomiting. There was also a history of mild exertional dyspnea for the past three years. On physical examination the blood pressure was 200 systolic and 100 diastolic. The eyes showed signs of acute congestive glaucoma. Aside from a slight enlargement of the heart the physical examination failed to reveal other significant abnormalities.

On March 23 the patient received 6 cc. of an old solution of sodium nitrite. The exact sodium nitrite content is not known but it was estimated to be between 0.5 to 2.0 Gm. The patient immediately vomited. In one-half hour the patient's blood pressure had fallen to 90 systolic and 50 diastolic. The respirations were

depressed, and slight cyanosis was noted that night. The next morning, March 24, the blood pressure had returned to 180 systolic and 100 diastolic. However, there was an extreme cyanosis of the body, most pronounced in the face and extremities. A sample of blood taken at this time showed 3.9 Gm. of methemoglobin per hundred cubic centimeters when examined spectroscopically. At 12:30 p. m., twenty-four hours after the original medication, 500 mg. of ascorbic acid was given intravenously. Within four hours there was a noticeable decrease in the amount of cyanosis. A further dose of 200 mg. of ascorbic acid was given intravenously. At 6.30 p. m. the cyanosis had disappeared clinically, and the methemoglobin level was 1.9 Gm. A total of 300 mg. was given in two doses intravenously during the remainder of the day. Fifty-six hours after initial therapy the methemoglobin level was 0.4 Gm. per hundred cubic centimeters.

COMMENT

Methemoglobin is the derivative formed by the oxidation of hemoglobin iron to the ferric state, with resultant loss of oxygen combining capacity. By the action of strong reducing agents methemoglobin iron is reduced to the ferrous state and the ability to form oxyhemoglobin restored.

In man, methemoglobinemia may be produced by drugs such as acetanilid and acetophenetidin, by oxidizing agents such as chlorates (used in gargles, matches and explosives), by nitrites, glyceryl-trinitrate and bismuth subnitrate (used in control of diarrhea) and by aniline dyes and their various derivatives. The formation of methemoglobin, in the absence of drug therapy, has been speculatively attributed to absorption of toxic products from the intestinal tract. There is, moreover, increasing evidence that the equilibrium hemoglobin ⇆ methemoglobin is shifted to the normal state by virtue of the glycolytic systems resident in the erythrocyte.[6] Any toxic product tending to inactivate or slow this glycolysis would bring about increasing concentrations of methemoglobin.

Cyanosis due to methemoglobinemia becomes clinically evident, according to Goodman and Gilman,[7] when the methemoglobin attains a level of 3 Gm. per hundred cubic centimeters of blood. Vigness and associates[8] found that cyanosis resulting from the administration of sulfanilamide became evident with a methemoglobin level of 12.3 per cent of the total blood pigment.

Treatment of methemoglobinemia has been undertaken in the past by the use of intravenously administered methylthionine chloride.

6. Drabkin, D. L.: Hemoglobin, Glucose, Oxygen and Water in the Erythrocyte, Science **101**:445, 1945.

7. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941.

8. Vigness, I.; Watson, C. J., and Spink, W. W.: Relation of Methemoglobin to the Cyanosis Observed After Sulfanilamide Administration, J. Clin. Investigation **19**:83, 1940.

According to Goodman and Gilman,[7] "methylene blue [methylthionine chloride] has two actions on hemoglobin. In high concentrations it converts the ferrous ion of the reduced hemoglobin to the ferric form, and thus methemoglobin is produced. Low concentrations of methylene blue or the chemically related thionine are capable in vivo of hastening the conversion of methemoglobin back to the form which once more can carry oxygen." It may be postulated that the action of methylthionine chloride in the reduction of methemoglobinemia is the result of the stimulation of tissue respiration, as indicated by the experiments of Warburg,[9] with the reduction of the methemoglobin accomplished by virtue of an increased enzymatic action of the dehydrogenases.

In contrast to methylthionine chloride, ascorbic acid has been shown to reduce methemoglobin in vitro.[10] The reducing properties of ascorbic acid are well known and have been investigated to a considerable extent. Considering the fact that sodium ascorbate has been administered intravenously in large doses without any deleterious effect and that it is a normal metabolite, it was suggested by one of us (B.D.P.) that the powerful reducing properties exhibited in vitro might be successful in vivo.

At present there is no evidence that methemoglobinemia occurs in subclinical ascorbic acid deficiency or frank scurvy. King and associates,[2f] who studied a patient with chronic methemoglobinemia, were able to demonstrate conclusively that as the ascorbic acid level of the plasma rose there was a concomitant drop in the methemoglobin of 50 per cent in five days with the oral administration of 300 mg. daily of ascorbic acid. The methemoglobin disappeared completely in twenty days under therapy. They then withheld ascorbic acid and were able to demonstrate that as the ascorbic acid fell to low levels the methemoglobin rose to its previous high levels. Denny[4a] and Graybiel[4b] were also able to demonstrate a lowering of the methemoglobin level by oral administration of ascorbic acid. We believe that the low ascorbic acid level encountered in the first case is more fortuitous than etiologic. It is to be emphasized that the use of ascorbic acid in the treatment of methemoglobinemia merely takes advantage of its reducing properties. The possibility that increased susceptibility to methemoglobinemia results from low intake of ascorbic acid requires investigation.

In the first patient the cause of the methemoglobinemia is unknown. So small a quantity as 0.7 mg. of glyceryl trinitrate is probably insufficient to cause the oxidation of approximately 30 per cent of the hemo-

9. Warburg, O.; Kubowitz, F., and Christian, W.: Ueber die katalytische Wirkung von Methylenblau in lebenden Zellen, Biochem. Ztschr. **227**:245, 1930.

10. Keise, M.: Biochem. Ztschr. **316**:264, 1944.

globin. The saline cathartic taken did not have, to our knowledge, any methemoglobinemia-producing substances. Argyria is not known to be associated with methemoglobinemia, nor was methemoglobin found in another patient with argyria. The nitrate ingested with the silver might cause cyanosis, but this medication had been stopped over six months prior to the patient's admission to the hospital: This case is presumed, then, to be a case of idiopathic methemoglobinemia or enterogenous cyanosis.

In the second patient "nitrite syncope" apparently developed from overdosage or from sensitivity to the drug. Although the exact amount of sodium nitrite given is unknown, the rapid development of cyanosis, which became pronounced eight hours later, shows clearly the relation of the drug therapy to the production of methemoglobin. Without doubt the presence of 35 per cent of the hemoglobin in an unusable form gave this woman a functional hypoxia which in the presence of a poor cardiovascular system was of serious consequence. Because of the severe clinical picture the intravenous use of ascorbic acid was preferred to oral therapy. The clinical evidence plus the results of the laboratory studies furnishes conclusive proof that the methemoglobin in the blood was reduced to hemoglobin. We wish to stress that in the second case the reduction was accomplished in a matter of hours rather than days by the intravenous use of ascorbic acid.

SUMMARY

Administration of ascorbic acid was followed by a rapid decrease in the concentration of methemoglobin in the blood of 2 patients showing cyanosis due to methemoglobinemia. At the same time there was prompt alleviation of other symptoms due to the methemoglobin. Ascorbic acid is far more desirable for this purpose than is methylthionine chloride, which may further increase the concentration of methemoglobin in the blood.

LÖFFLER'S SYNDROME ASSOCIATED WITH CREEPING ERUPTION (CUTANEOUS HELMINTHIASIS)

Report of Twenty-Six Cases

COLONEL D. O. WRIGHT
AND
MAJOR EDWIN M. GOLD
MEDICAL CORPS, ARMY OF THE UNITED STATES

WE RECENTLY reported 9 cases[1] of transitory, migratory pulmonary infiltration with peripheral eosinophilia and paucity or absence of systemic manifestations, fulfilling the criteria of Löffler's syndrome. In these cases the syndrome complicated creeping eruption, which was offered as a previously unreported cause of pulmonary infiltration. The purpose of the present report is to record 17 additional cases of pulmonary infiltration complicating creeping eruption, making a total of 26 cases of Löffler's syndrome occurring among 76 cases of creeping eruption.

A report of this larger series is warranted for the following reasons:

(1) to establish creeping eruption as an additional etiologic factor in the production of the so-called Löffler's syndrome;

(2) to prove that creeping eruption is not always a localized cutaneous disease;

(3) to forge an additional link in the chain of circumstantial evidence that the pathogenesis of Löffler's syndrome is an allergic phenomenon.

CREEPING ERUPTION

Creeping eruption (cutaneous helminthiasis), which is endemic in the southeastern coastal regions of the United States, has been considered a purely cutaneous disease.[2] It is characterized by serpigi-

1. Wright, D. O., and Gold, E. M.: Loeffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis), J. A. M. A. **128**:1082-1083 (Aug. 11) 1945.

2. (*a*) Cecil, R. L.: A Textbook of Medicine, ed. 6, Philadelphia, W. B. Saunders Company, 1943. (*b*) Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939. (*c*) Yater, W. M.: The Fundamentals of Internal Medicine, ed. 3, New York, D. Appleton-Century Company, Inc., 1942. (*d*) Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 2, Philadelphia, Lea & Febiger, 1940. (*e*) Hume, E. E.: Creeping Eruption in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1940, vol. 3, p. 695.

nous elevated reddish tunnels or burrows, usually occurring on the exposed surfaces of the skin (fig 1). Kirby-Smith [3] first suggested the nematodal origin of these lesions. Kirby-Smith, Dove and White [4] proved that the filariform larvae of Ancylostoma braziliense (hookworm of dogs and cats) produced these lesions. They firmly established the life cycle of this nematode and the epidemiology of the disease. The dog and the cat are natural hosts for this nematode, and they inoculate the soil with their feces containing the ova of A. braziliense. The active filariform larvae from these ova remain viable for long periods in sandy soil that is warm and moist, awaiting an opportunity for contact with the skin of human beings. This opportunity occurs most frequently in the vicinity of swimmers, children, soldiers, plumbers and others whose occupation necessitates contact with the soil. Within a few hours after the larva contacts the skin, a pruritic urticarial-like lesion develops at the site of penetration. In seven to seventy-two hours a serpiginous reddish elevated tunnel appears, which increases in length day after day as the larva migrates in the layers of the skin. Intense itching is the rule, and mild cellulitis about the lesion, due to secondary infection, is not uncommon.

Lesions on the feet are frequent and are often misdiagnosed as epidermophytosis and treated with salicylic acid, the effect of this adding to the acute inflammation and masking the classic appearance of the lesion.

Experimental proof of the production of creeping eruption by A. braziliense has been offered by Shelmire [5] and Dove.[6] Shelmire applied pure cultures of such larvae to the unbroken skin of human beings, and the penetrations of the larvae produced typical lesions of creeping eruption. White and Dove also produced the classic linear serpiginous burrows of creeping eruption by applying cultures of the larvae of A. braziliense to human skin, but the application of the larvae of Ancylostoma canium produced a papular lesion without the linear burrows. We believe that the creeping eruptions in all our cases were

3. Kirby-Smith, J. L.: Creeping Eruption, J. Florida M. A. **4**:95-100 (Oct.) 1917.

4. (*a*) Kirby-Smith, J. L.; Dove, W. E., and White, G. F.: Creeping Eruption, Arch. Dermat. & Syph. **13**:137-175 (Feb.) 1926; (*b*) Some Observations on Creeping Eruption, Am. J. Trop. Med. **9**:179-193 (May) 1929. (*c*) White, G. F., and Dove, W. E.: The Causation of Creeping Eruption, J. A. M. A. **90**: 1701-1704 (May 26) 1928.

5. Shelmire, B.: Experimental Creeping Eruption from a Dog and Cat Hookworm (A. Braziliense), J. A. M. A. **91**:938-943 (Sept. 29) 1928.

6. Dove, W. E.: Further Studies on Ancylostoma Braziliense and the Etiology of Creeping Eruption, Am. J. Hyg. **15**:664-711 (May) 1932.

caused by A. braziliense because typical linear burrows were present in each of the cases (fig. 1).

Shelmire also showed that repeated cultures of the stool from his 7 spontaneously infected and his 16 experimentally infected patients failed to show intestinal infection from A. braziliense. Similarly in our series, repeated examinations of the stool have failed to disclose the presence of the ova or the parasite in the stool. This bears out the general consensus in the literature.

Fig. 1.—The clinical appearance of the classic serpiginous vesicular burrows.

LOEFFLER'S SYNDROME

Since Löffler's [7] original description of the syndrome of transitory pulmonary infiltration associated with peripheral eosinophilia and

7. Löffler, W.: Zur Differential-Diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk. **79**: 368-382, 1932.

paucity or absence of systemic manifestations, a voluminous literature has developed. The most striking observation from a perusal of this literature is the multitude of etiologic agents. Löffler [8] expressed the opinion that this condition represented a tuberculous process on a pathergic basis. In 1935, Engel [9] ascribed its production to the inhalation of pollen from the privet shrub. Meyer [10] expressed the belief that the inhalation of pollen of the Convallaria in Europe was the etiologic factor. Recently, Harkavy [11] and Hansen-Pruss and Goodman [12] reported on Löffler's pneumonia complicating chronic asthmatic states. Other etiologic factors that have been reported are: Ascaris,[13] Trichuris trichiura,[14] Strongyloides,[15] Taenia saginata,[16] Fasciola hepatica,[17] Endamoeba histolytica,[18] trichinas,[19] brucellas [20] and

8. Löffler, W.: Die flüchtigen Lungeninfiltrate mit Eosinophilie, Schweiz. med. Wchnschr. **66**:1069-1078 (Nov. 7) 1936.

9. Engel, D.: (*a*) Ueber eine eigenartige anaphylaktische Erkrankung der Lumge, Beitr. z. Klin. d. Tuberk. **87**:239-250, 1935; (*b*) Zur Frage des anaphylaktischen Frühjarsödems der Lunge: Bemerkungen zu einer Arbeit von W. Löffler, ibid. **89**:323-326, 1937.

10. Meyer, H. E.: Zur Kenntnis flüchtiger mit Eosinophilie im Blut einhergehender Lungeninfiltrate, Med. Welt **11**:1808-1810 (Dec. 25) 1937.

11. Harkavy, J.: Vascular Allergy: III., J. Allergy **14**:507-537 (Nov.) 1943.

12. Hansen-Pruss, O. C., and Goodman, E. G.: Allergic Pulmonary Consolidations, Ann. Allergy **2**:85-108 (March-April) 1944.

13. (*a*) Baumann, H.: Eosinophilic Pleurisy with Transitory Eosinophilic Pulmonary Consolidation, Schweiz. med. Wchnschr. **74**:326 (April 1) 1944; abstracted, Trop. Dis. Bull. **49**:859-860 (Oct.) 1944.

14. Miller, H.: Transitory Lung Infiltrations Accompanied by Eosinophilia, New England J. Med. **232**:7-10 (Jan. 4) 1945.

15. Berk, J. E.: Transitory Pulmonary Infiltrations, Correspondence, J. A. M. A. **127**:354-355 (Feb. 10) 1945.

16. Benda, R., and Weinberg, L.: Two Cases of Loeffler's Syndrome, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:24-27 (Feb. 14) 1940.

17. Lavier, G.; Bariety, M., and Caroli, J.: Distomatose hépatique et syndrome de Loeffler, Paris méd. **1**:434-439, 1939.

18. Hoff, A., and Hicks, H. M.: Transient Pulmonary Infiltration: A Case with Eosinophilia (Loeffler's Syndrome) Associated with Amebiasis, Am. Rev. Tuberc. **45**:194-199 (Feb.) 1942.

19. Slowey, J. F.: A Case of Transient Pulmonary Infiltration (Loeffler's Syndrome) Associated with Trichiniasis, Ann. Int. Med. **21**:130-135 (July) 1944.

20. Elsom, K. A., and Ingelfinger, F. J.: Eosinophilia and Pneumonitis in Chronic Brucellosis: A Report of Two Cases, Ann. Int. Med. **16**:995-1002 (May) 1942.

azosulfamide.[21] Because of our observations we add cutaneous helminths as an additional cause. This diversified list of etiologic factors lends credence to the view that Löffler's syndrome is an allergic phenomenon.

CLINICAL DATA

During the summers of 1943 and 1944 we observed 76 cases of creeping eruption with classic cutaneous lesions. It was possible to study 52 of these cases for fourteen days or longer. During this period of study in 26 of the 52 cases there developed transitory, migratory pulmonary infiltration and peripheral eosinophilia, with almost complete absence of clinical signs or symptoms of systemic disease.

TABLE 1.—*Summary of Data from Investigative Procedures*

	Symptoms (76 Cases)	
	No. of Cases	Per Cent of Series
Itching	65	85.5
Cough	9	11.8
Infection *	8	10.5
	Laboratory Data (76 Cases)	
	No. of Tests	Results
Eosinophil count (blood)	507	High, 51% Low, 1%
Eosinophil count (sputum)	381	High, 90% Low, 0%
Examination of the stool	441	All neg. for A. braziliense E. coli..... 6 E. nana..... 4 N. americanus..... 1 G. lamblia..... 3
Sedimentation rate	395	Elevated* in 8 cases
Cutaneous tests	57	75.5% positive 24.5% negative

* In these cases there was secondary infection with local cellulitis.

Our investigative procedures in these cases, summarized in table 1, consisted of roentgenographic examination of the chest every third day, determinations of peripheral and sputal eosinophilia, study of the sedimentation rate, examinations of the stool for ova and parasites and intradermal testing with the antigens from Ascaris lumbricoides and Trichinella spiralis.

21. Ellis, R. V., and McKinlay, C. A.: Allergic Pneumonia, J. Lab. & Clin. Med. **26**:1427-1432 (June) 1941.

Data on 4 representative cases have been summarized in tables 2, 3, 4 and 5.

TABLE 2.—*Data on Representative Case* *

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
5	9/26/44	18	10	None	6.0
11	10/ 2/44	32	60	None	1.5
27	10/18/44	48	0	Lower lobe of the right lung	2.5
33	10/24/44	30	0	None	3.0
47	11/ 7/44	18	Q.N.S. †	None	3.0

* Case 55. The patient was admitted to the hospital on the fifth day of the cutaneous disease with burrows generalized over the trunk anteriorly and posteriorly and over the extremities, upper and lower.

† Q.N.S. means quantity of sputum was not sufficient for a count of eosinophils to be made.

TABLE 3.—*Data on Representative Case* *

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
11	9/29/44	13	25	None	1.0
14	10/ 2/44	19	25	None	1.0
32	10/20/44	2	0	Right costophrenic angle	12.0
36	10/21/44	3	0	Right costophrenic angle	14.0
43	10/31/44	11	0	None	5.5
50	11/ 7/44	6	0	None	3.0

* Case 48. The patient was admitted to the hospital on the eleventh day of the cutaneous disease, with itching burrows over both buttocks.

TABLE 4.—*Data on Representative Case* *

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
11	7/13/44	4	35	None	...
20	7/22/44	11	0	Lower lobe of the left lung	1.0
26	8/28/44	19	5	Lower lobe of the left lung (—)	1.0
32	8/ 3/44	22	8	None	3.0
	9/ 6/44	10	30	None	0.5

* Case 25. The patient was admitted to the hospital on the eleventh day of the creeping eruption over the left side of the back and the posterior surfaces of the upper parts of both arms. The patient complained only of itching. On admission to the hospital the patient had a diagnosis of herpes.

TABLE 5.—*Data on Representative Case* *

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
11	10/11/44	23	0	.....	1.5
20	10/20/44	28	0	Upper lobe of the left lung	5.0
24	10/24/44	..	0	Upper lobe of the left lung	...
32	11/ 1/44	21	0	None	12.0
42	11/11/44	19	0	None	11.0
60	11/29/44	15	0	None	5.0

* Case 47. The patient was admitted to the hospital on the eleventh day of the cutaneous disease, with itching burrows over the right arm and forearm.

Clinical Course.—All patients were afebrile except 8 in whom cellulitis developed, due to secondary infection of the cutaneous lesions. Physical findings were minimal or absent. Slightly decreased resonance, roughened breath sounds and an insignificantly increased respiratory rate, when present, were the only positive thoracic findings. Rales were not heard at any time. Sputum was scant or absent. Except for the local cutaneous irritation and a mild cough that occurred in 9 cases, the patients were not aware of any illness.

Eosinophilia.—Differential blood smears, examined every third day during the period of observation, revealed an eosinophil count ranging from 1 to 51 per cent. The degree of the eosinophilia approximated the extent of the pulmonary consolidation and tended to persist for four to six weeks after the consolidation

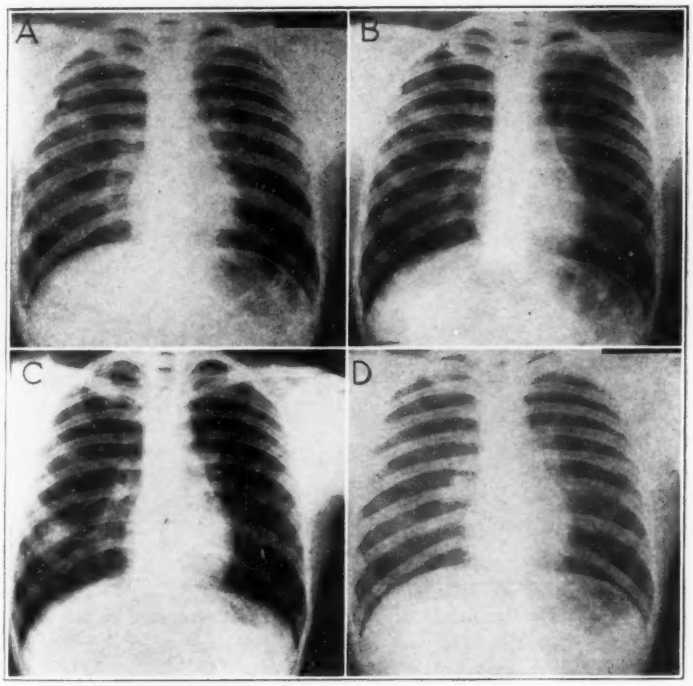

Fig. 2.—The migratory character of the pulmonary lesions in a representative case.

had subsided. This observation is in agreement with those of other investigators.[12] Examinations of the sputum for eosinophils were done every third day, and the count ranged from 0 to 90 per cent. The height of eosinophilia approximated the degree of pulmonary consolidation and also persisted for four to six weeks, despite subsidence of roentgenographic evidence of pulmonary consolidation.

Roentgenologic Studies.—Roentgenographic examination of the chest revealed a patchy infiltration, transient and often migratory in nature, usually not appearing before the seventh day of the cutaneous eruption. When the cutaneous lesions

were untreated, the pulmonary infiltrations continued on a migratory course over a period of weeks. The transient and often migratory character of the lesions is shown by representative roentgenograms of the chest in figure 2. The shadows varied in size from isolated parenchymal lesions, approximately 2 by 3 cm. (fig. 2 *A*), to patchy involvement of approximately 75 per cent of the pulmonary fields (fig. 3). The supraclavicular fields remained clear in all cases. Cavitation was not seen. Demonstration of transient or migratory infiltration by serial roentgenograms of the chest prevents an erroneous diagnosis of pulmonary tuberculosis or sarcoid.

Examinations of the Stool.—A total of 441 examinations of the stool were performed by Faust's zinc sulfate centrifugal flotation technic. Nematodal ova or parasites were not found except in 1 case in which the patient harbored ova of Necator americanus, but in this patient pulmonary infiltration did not develop. Two hundred and four examinations were performed for the 26 patients with

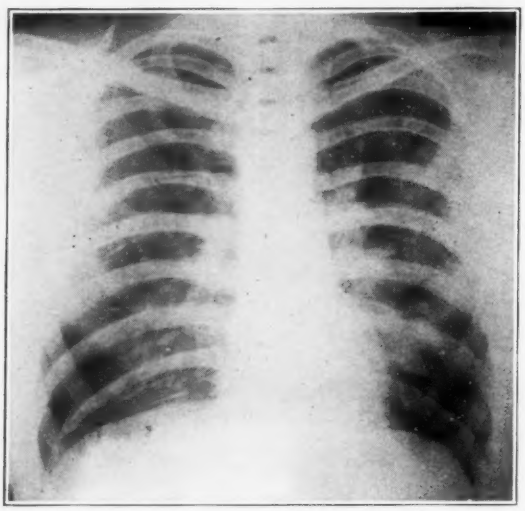

Fig. 3.—The greatest degree of pulmonary involvement seen in the series.

Löffler's pneumonia. Thirteen of them had a total of 172 examinations of the stool over a period of six weeks or more, which is sufficient time to eliminate the possibility of concomitant infestation with the hookworm of human beings. The following intestinal parasites were present in patients with pulmonary infiltration: Endamoeba coli and Endamoeba nana in 1 patient each and Giardia lamblia in 2 patients.

Sedimentation Rate.—The sedimentation rate is of value in differential diagnosis. A total of 395 determinations of sedimentation rate were made by the Wintrobe method. All readings were approximately normal except in 8 cases. In 6 of these the abnormal readings were due to the secondary infection and cellulitis present about the cutaneous lesions, and they returned to normal as the cellulitis cleared, despite the persistence of pulmonary lesions. In the 2 remaining

cases the rapid sedimentation rates coincided with the pulmonary infiltration, but they returned to normal before the infiltration cleared.

Cutaneous Tests.—Brunner indicated that testing with extracts of A. lumbricoides and T. spiralis was sufficient for the diagnosis of any nematodal infestation. Intradermal tests with aqueous extracts of Ascaris and Trichina were performed for 57 patients. Seventy-five per cent of these patients showed a positive reaction to one or both of the antigens. This suggests that A. braziliense, a member of the roundworm group, had antigenetically sensitized the host and that this may be the causative factor in producing the transitory, migratory pulmonary infiltration. No correlation between the degree of cutaneous sensitivity shown in the test and the extent of pulmonary infiltration was observed.

COMMENT

The pulmonary infiltrations in this series of cases were not caused by concomitant infestation with the hookworms of human beings because:

1. Classic linear burrows were present in all cases.

2. Neither nematodes nor ova were found in 204 stool examinations. Thirteen of the patients with pulmonary lesions had repeated examinations (a total of 172) for a period of more than six weeks.

3. No nematodal larvae of any type were found in 381 examinations of sputum.

Our failure to identify the ova or the parasites of A. braziliense in 441 examinations of the stools confirms the reports of others [22] that in human beings intestinal infestation with ancylostomes of this species is almost unknown. However, it should be pointed out that Bonne [23] observed Ancylostoma invading the wall of the human intestine in a total of 10 cases. In only 1 case was the invading nematode A. braziliense. He suggested that perhaps the reason for the inability to find the larvae of A. braziliense in the stool was due to the fact that these larvae have the habit of burrowing either subepidermally in the skin or submucosally in the intestinal tract.

These observations lead to three possibilities concerning the pathogenesis of the pulmonary infiltrations associated with creeping eruption.

1. In view of Boone's reports, the pulmonary infiltrations could be caused by transpulmonary larval migration, just as with Necator americanus or Ancylostoma duodenale.

2. If we ignore Boone's reports and adhere to our observations and the reports of others of failure to find A. braziliense in the

22. Footnote 4. Shelmire.[5] Dove.[6]

23. Bonne, C.: (*a*) Invasion of the Submucosa of the Human Small Intestine by Ancylostoma Braziliense, Am. J. Trop. Med. **17**:587-594 (July) 1937; (*b*) Invasion of Wall of Human Intestine by Ancylostomes, ibid. **22**:507-509 (Sept.) 1942.

stools of patients with creeping eruptions, the pulmonary lesions could be caused by the larvae reaching the lung and dying there, thus failing to reach the intestinal tract.

3. A. braziliense remaining subepidermal elaborates an exotoxin which antigenically sensitizes the host, as suggested by the intradermal reactions to test antigens of Ascaris and/or Trichina, and the lung as shock tissue reacts to the blood-borne antigens from the larvae in the cutaneous lesions.

Regardless of which mechanism proves to be correct, the pulmonary infiltrations are caused by an antigenic response to the presence of either the larvae or its blood-borne exotoxin.

CLINICAL SIGNIFICANCE AND DIFFERENTIAL DIAGNOSIS

Since there is little objective and no subjective evidence of pulmonary or systemic disease, the chief clinical significance is in the differential diagnosis. If the clinician is not aware of the possibility of pulmonary infiltration complicating creeping eruption, an erroneous diagnosis of virus pneumonia, pulmonary tuberculosis or sarcoid may be made. The results of the treatment of the cutaneous lesions, serial roentgenograms of the chest and normal sedimentation rates will differentiate these conditions.

TREATMENT

Treatment of the cutaneous lesions consists of the application of ethyl chloride, which is sprayed for thirty seconds daily over an area 4 to 5 cm. in diameter about the ends of the tunnels. If the cutaneous lesions remain untreated, the larvae continue their migration in the skin for several weeks, and the transient, migratory pulmonary infiltrations may continue. In 1 untreated patient pulmonary lesions developed fifty-nine days after the appearance of cutaneous lesions, and the infiltration persisted for thirty days. Roentgenographic evidence of pulmonary infiltration promptly subsides when the cutaneous lesions are properly treated.

SUMMARY

Pulmonary lesions compatible with the diagnosis of Löffler's pneumonia occurred in 26 of 52 cases of creeping eruption. The lesions were observed by means of serial roentgenograms of the chest for fourteen days or more.

Present Address: Medical Arts Bldg., Birmingham, Ala.

TREATMENT OF GUMMATOUS HEPATIC SYPHILIS WITH PENICILLIN

Report of Two Cases *

HAROLD A. TUCKER, M.D.
AND
DAVID D. DEXTER, M.D.
BALTIMORE

THIS is the first report dealing with penicillin as used in the treatment of gummatous hepatic syphilis. Two cases are presented.

REPORT OF CASES

CASE 1.—A 49 year old Negro housewife was admitted to the hospital on Oct. 25, 1943, because of right-sided abdominal and thoracic discomfort of four years' duration and soreness of the right knee of two years' duration. The past and family histories were not pertinent except that a blood serologic test for syphilis had been negative in 1929. The patient said that she had contracted no venereal diseases.

For four years she had had attacks of "pleurisy" on the right side, which had at times required medical care. One and a half years before admission she began to be troubled with pain and "tightness" in the right upper quadrant of the abdomen, together with a feeling of fulness in the region of the liver. About every two months she had attacks with colic-like discomfort in this area which lasted a day or so and which were associated with constipation but never with nausea, vomiting, jaundice, light-colored stools or dark urine. About two years prior to entering the hospital she had fallen and hurt her right knee; it had become swollen, hot and tender. This condition had gradually become worse until, at the time of admission, she limped noticeably and had "shooting pains" in the involved parts. The left knee, without trauma, had become similarly affected, although to a lesser degree. During the preceding year she had lost about 16.3 Kg. (36 pounds) in weight and had become so generally debilitated that hospitalization was thought necessary.

Physical examination revealed an emaciated, chronically ill Negro woman. Her appearance is shown in figure 1*A*. The blood pressure was 112 mm. of mercury systolic and 64 mm. diastolic. A loud blowing systolic murmur was heard over the entire precordium, and the aortic second sound was accentuated. The lungs seemed normal. The abdomen was remarkable, the liver being enlarged to between 11 and 12 cm. below the right costal margin in the midclavicular line. It was tender, and its anterior surface presented several large nodules. No bruit could be heard over this mass. About 4 cm. below the costal margin, the spleen

* From the United States Public Health Service and the Johns Hopkins University Venereal Disease Research and Post-Graduate Training Center, Baltimore.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins University.

was also felt. There was no evidence of ascites, dilated superficial veins or hemorrhoids. The right knee joint was somewhat swollen and tender; the patella was floating, and there was excess fluid in the synovial cavity. The patella was irregular in contour and was exquisitely sensitive when compressed, although it could be painlessly moved about. There was also moderate tenderness over the lower third of the femur and the upper third of the tibia. Similar conditions of lesser severity were present in the left knee. The neurologic examination revealed no abnormalities except generalized hyperreflexia.

Laboratory tests yielded the following data: The Eagle serologic test for syphilis was positive; the flocculation titer was 128 units. A complement fixation test and the Frei test for lymphogranuloma venereum were negative, as was the routine Ito-Reenstierna test for chancroid. There was microcytic anemia, with 4,210,000 erythrocytes per cubic millimeter of blood, as well as achromia, anisocytosis and poikilocytosis. There was 7.0 Gm. of hemoglobin per hundred cubic centimeters of blood. The leukocyte count was not abnormal, and the icteric index was 5.0

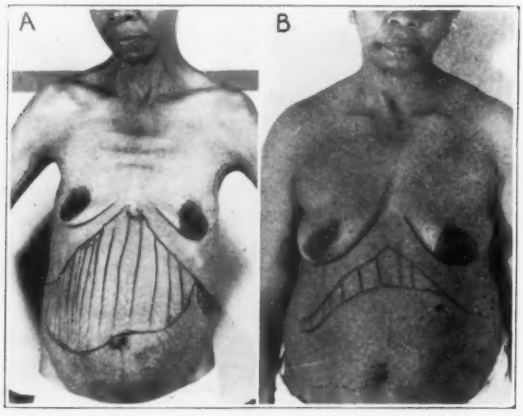

Fig. 1 (case 1).—Response of benign late syphilis (gummas) of the liver to penicillin therapy: *A*, before treatment; *B*, six hundred and eighty-six days after initiation of therapy.

units. A urinalysis done on the patient's admission to the hospital showed 3 plus urobilin but no bilirubin; the results of subsequent tests were within normal limits. The results of chemical analyses of the blood were reported as follows: total serum protein, 8.19 Gm. per hundred cubic centimeters; albumin-globulin ratio, 0.72; cholesterol, 200 mg. per hundred cubic centimeters of blood. The serum phosphatase activity was 16.5 Bodansky units per hundred cubic centimeters of serum. The prothrombin time was normal, as were the results of the hippuric acid and sulfobromophthalein sodium tests of hepatic function. A cephalin flocculation determination was strongly positive. In the congo red test for amyloidosis 91 per cent of the dye was excreted in one hour (a normal result). Subsequent variations in significant laboratory and clinical data are presented in figure 2.

Roentgenograms demonstrated areas of radiolucency in the patellas and proliferative activity around the middle thirds of both femurs. These were characterized by both destruction and proliferation of bone and were interpreted as syphilitic in origin (fig. 3 *A*).

The huge, nodular, sensitive liver, the associated syphilitic osteoperiostitis, the positive blood serologic test and a temperature which ranged as high as 103.2 F. (rectal) were considered to be evidence justifying the diagnosis of multiple hepatic gummas. The splenomegaly was not inconsistent with this diagnosis. The long duration of symptoms with the comparatively minor impairment of general health was regarded as a decisive factor in the diagnosis. The use of penicillin was undertaken partly as a therapeutic test, with the expectation that the tenderness and the fever would disappear rapidly but that a rapid diminution in the size of the liver was not to be expected.

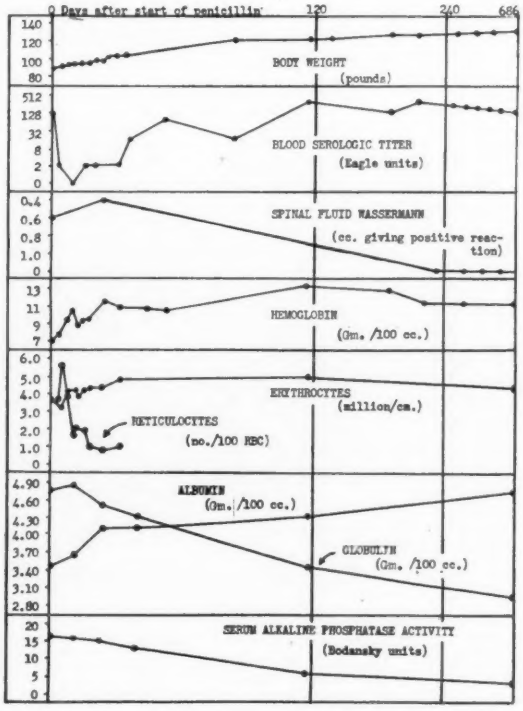

Fig. 2 (case 1).—Improvement following penicillin therapy.

On Oct. 29, 1943, the administration of sodium penicillin in isotonic solution of sodium chloride was begun; the patient received 5,000 Oxford units intramuscularly every three hours for sixty-four injections in eight days, a total of 320,000 units. This dose was arbitrarily selected on an experimental basis only. On October 31 the temperature became normal and remained normal (fig. 4). The tenderness previously associated with the enlarged liver and the knees had dramatically diminished. No changes, however, could be noted in the size of the liver or the spleen. A pronounced reticulocyte response occurred, and on November 15 the hemoglobin content had risen to 9.4 Gm. per hundred cubic centimeters of blood. The excess of synovial fluid was now gone from the joint cavity of the right knee.

By November 24, twenty-seven days after the start of penicillin therapy, the spleen could no longer be felt.

Because of the excellent initial response to this antibiotic substance, the low total dose originally employed and the potential gravity of the patient's illness, a second course of penicillin was thought desirable. On November 26, sodium penicillin therapy was resumed; 10,000 Oxford units were given intramuscularly every three hours for sixty injections in seven and a half days, to a total of 600,000 units. There was no additional clinical improvement during this second course. Altogether, in the two courses, 920,000 units of penicillin was administered.

At the time of discharge from the hospital, on December 8, she had regained 4.5 Kg. (10 pounds) in body weight, and even weight bearing caused no discomfort in her knees. The hemoglobin had risen to 10.6 Gm. per hundred cubic centimeters of blood and the albumin-globulin ratio to 0.96. The size of the liver had not appreciably lessened.

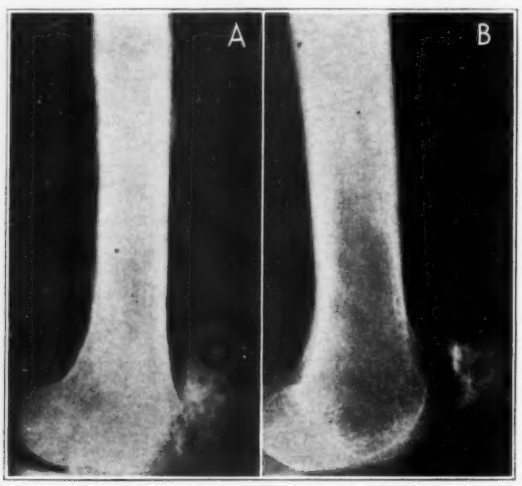

Fig. 3 (case 1).—Response of osteoperiostitis to penicillin therapy. *A*, right femur and patella prior to treatment; *B*, two hundred and forty-five days after start of treatment, illustrating distinct reduction in the original proliferative periostitis. Roentgenograms taken six hundred and eighty-six days after penicillin was begun showed little further change.

Frequent follow-up examinations were carried out in the outpatient department. These revealed a steady, sustained improvement. One hundred and seventeen days after the start of therapy (Feb. 22, 1944) the patient was again admitted to the ward for evaluation of her status. Her weight was now 55.8 Kg. (123 pounds), a total gain of 14.1 Kg. (31 pounds), and she appeared younger and more vivacious; she had had her hair dyed. The edge of the liver extended only 8 cm. below the right costal margin in the midclavicular line and, except for the residual irregular contour of the patellas, examination of the lower extremities revealed no abnormalities.

During the next four months the edge of the liver receded another centimeter, and in June 1944 roentgenograms of the femurs showed considerable improvement over the ones taken prior to treatment; the appearance of the patellas was essen-

tially unchanged (fig. 3 *B*). On Feb. 1, 1945, the liver measured only 5 cm. below the costal margin, and the general status of the patient remained excellent.

The most recent examination, six hundred and eighty-six days after the initiation of penicillin treatment, disclosed a well nourished Negro woman weighing 61.7 Kg. (136 pounds) (fig. 1 *B*). She felt entirely well. The edge of the liver in the midclavicular line was only 3 cm. below the costal margin, and no tenderness was elicited over it or over the femurs or the patellas. Although the flocculation titer of the Eagle test for syphilis was 128 units, the spinal fluid gave no evidence of syphilis. Hematologic studies, including albumin, globulin and hemoglobin determinations and an erythrocyte count, showed that the original improvement had been maintained. Serum alkaline phosphatase activity, elevated at the time of initiation of treatment, was normal. Roentgenograms did not demonstrate significant osseous changes when compared with those last taken.

CASE 2.—A 15 year old white school girl was first admitted to the surgical service of the Johns Hopkins Hospital on April 25, 1944, complaining of a painful, tender lump in the right upper part of her abdomen of two years' duration. She was the third of 13 children, 11 of whom were living. As subsequent investigations brought to light, she had been given some antisyphilitic therapy when about 1 year

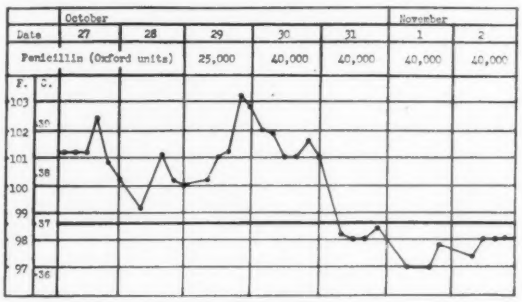

Fig. 4 (case 1).—Response of temperature to penicillin therapy.

of age. Both parents had also had some treatments by injection. The past history was otherwise noncontributory except that menses had not yet begun.

About two years previously, she had felt a spontaneous sharp pain and had noted a firm, tender tumor in the right upper quadrant of her abdomen. Thereafter, although the pain was only occasionally present, the mass continued to increase in size, as observed by herself and her family, and she began to be troubled by a sensation of epigastric fulness for one or two hours after eating. One year prior to her admission to the hospital she had become unable to concentrate on her work or to sleep well and had stopped attending school. Four days before entry she had turned over in bed and had experienced a severe pain on the right side over the abdominal mass, which persisted with movement or pressure and did not radiate. When she was immobile, her distress would pass entirely away. No jaundice, nausea, vomiting, diarrhea, constipation or melena had been noted, nor had there been weakness or faintness.

On physical examination the patient was an undernourished white girl, pale but not icteric, with poorly developed secondary sex characteristics and a prominent mass in the right upper quadrant of the abdomen. The teeth were carious. Interstitial keratitis was not found (slit lamp examination). Dilated superficial veins were present over the abdomen and the lower part of the thorax. Hepatic

dulness extended from the fourth interspace on the right to the level of the umbilicus; no bruit could be heard, nor could pulsations be distinguished in this region. A distinct nodule, measuring about 5 by 7 cm., firmly attached to, or an integral part of, the anterior surface of the liver, could be seen and felt midway between the costal margin and the umbilicus. The spleen was firm, nontender and easily palpable just above the iliac crest, as illustrated in figure 5 *A*.

Laboratory examinations yielded the following data: The hemoglobin was 9.5 Gm. per hundred cubic centimeters of blood. There were 5,300 leukocytes per cubic millimeter of blood and the differential blood cell count was normal. Bilirubin was present in a concentration of less than 0.8 mg. per hundred cubic centimeters of blood, and no bile was demonstrated in the urine. The albumin-globulin ratio was 0.88, and the total serum protein was 8.81 Gm. per hundred cubic centimeters of blood. The prothrombin time was normal, as was the sulfobromophthalein sodium test. The Eagle flocculation reaction for syphilis was positive.

It was felt by the surgeons that an exploratory operation was indicated in view of the possibility of neoplastic or parasitic disease. On May 1, 1944, cyclopropane

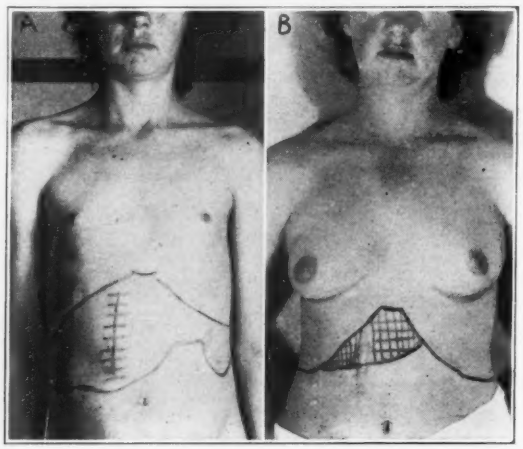

Fig. 5 (case 2).—Response of multiple hepatic gummas to penicillin therapy: *A*, before treatment; *B*, four hundred and ninety-one days after initiation of therapy.

and oxygen anesthesia being used, a laparotomy was performed by Dr. George Duncan. The surface of the right lobe of the liver was described as being studded with large firm nodules, one particularly prominent one causing the visible mass previously noted. The inferior surface of the right lobe had a similar appearance, the process apparently extending through the entire thickness of the organ. The cut surface of the largest nodule, from which a biopsy specimen was taken, was grayish yellow, and the mass itself was rubbery in consistency. The enlarged spleen was granular, with rounded edges. The pathologic report on the microscopic examination of the tissue sections (fig. 6) described large areas of necrosis surrounded by fibrous tissue, occasional scattered solitary tubercles and a slight infiltration of mononuclear cells. Acid-fast stains failed to demonstrate bacilli, and silver impregnation methods did not disclose Treponema pallidum. The pathologist's impression was "probable gumma of the liver."

The postoperative course was uneventful, and on May 10 the patient was transferred to the medical service for the penicillin treatment of congenital syphilis and multiple gummas of the liver. Blood serologic tests for syphilis elicited positive reactions; in the Eagle test the flocculation titer was 512 units as shown graphically in figure 7. No cells were seen in the cerebrospinal fluid, and the protein content was normal (19 mg. per hundred cubic centimeters), but the Wassermann reaction was positive with 1.0 cc. of fluid. A negative colloidal mastic curve was reported. The patient's anemia was more profound than before operation. The corrected sedimentation rate (Wintrobe) was 25 mm. per hour. Hippuric acid

Fig. 6 (case 2).—Biopsy specimen taken prior to penicillin treatment: *A*, low power magnification showing transition from typical area of caseous necrosis to one with epithelioid and infiltrated mononuclear cells, *B*, higher magnification of transition zone (× 200).

synthesis was subnormal (0.62 Gm.), and the sulfobromophthalein sodium test disclosed 12 per cent retention of dye after thirty minutes. Reticulocyte determinations and values for blood nonprotein nitrogen and cholesterol were normal, as were roentgenograms of the long bones. Serum alkaline phosphatase activity was elevated (23.8 Bodansky units per hundred cubic centimeters of serum). Roentgenograms of the thorax and barium sulfate studies of the gastrointestinal tract showed no abnormalities except distortion due to the enlargement of liver and spleen.

Administration of sodium penicillin was begun on May 11. The patient was given 40,000 units in isotonic solution of sodium chloride intramuscularly every three hours for eighty injections, a total of 3,200,000 Oxford units in ten days. The temperature was elevated to 100.4 F (rectal) fifteen hours after the start of treatment. This was interpreted as a possible Herxheimer reaction. She was subsequently afebrile, and therapy was completed without incident. When she was discharged from the ward, distinct general improvement was noticeable. No change was demonstrable in the size of the liver or in that of the spleen, but tenderness over these organs had completely disappeared. The corrected sedimentation rate had fallen to 13 mm. per hour. The total serum protein was slightly decreased to 8.19 Gm. per hundred cubic centimeters of blood, and the albumin-globulin ratio had risen to 1.18. Serum alkaline phosphatase activity was now reported as 17.0 Bodansky units per hundred cubic centimeters of serum.

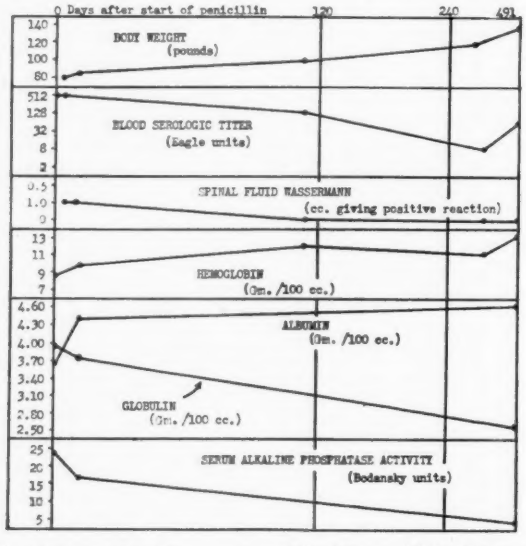

Fig. 7 (case 2).—Improvement following penicillin therapy.

This patient lives at some distance from Baltimore, and visits to the clinic were infrequent. She was next seen in August 1944. The liver then extended 5 cm. below the right costal margin in the midclavicular line. The spleen was no longer palpable. Her color had improved, and she weighed 44.9 Kg. (99 pounds). In the Eagle test for syphilis the flocculation titer had fallen to 128 units, and the Wassermann test of her spinal fluid was negative. In April 1945 the liver extended 4 cm. below the costal margin and could be felt only in the midclavicular line. She remained completely asymptomatic. The Eagle test for syphilis showed a further decrease of titer to 8 units, and the Wassermann test of the spinal fluid remained negative.

On September 13 this patient was again examined. In the four hundred and ninety-one days since the start of treatment her general condition had vastly improved, as shown in figure 5 *B*; menses had begun. The liver was practically normal in size, its edge being palpable between 2 and 3 cm. below the right costal

margin in the midclavicular line. The organ could be percussed out but not definitely felt on the left side of the laparotomy scar. The Eagle test showed the flocculation titer increased to 64 units, but the Wassermann test of the spinal fluid remained negative. The results of chemical and microscopic studies of the blood were all within normal limits, and there was no clinical evidence of hepatic dysfunction.

COMMENT

Active late syphilis of the liver is a condition rarely demonstrated clinically. The initial and essential lesion is the gumma, which arises in a highly localized or focal manner. As emphasized by Hahn,[1] "A focal process, in an organ with the functional reserve and capacity for regeneration of the liver, can rarely be expected to produce symptoms either of hepatic insufficiency or of portal failure. . . ." During the active stage of gummatous involvement fever, pain and tenderness and, as a rule, hepatic enlargement are present; general well-being is usually out of proportion to the duration of symptoms referable to the liver. As with the clinical observations, laboratory and roentgenographic studies do not permit more than a presumptive diagnosis.

Two methods are available for proving the presence of active hepatic gummas. The first and more reliable method is to make a biopsy, a procedure not without risk. The second method is to employ a therapeutic test. Iodides and mercury, bismuth and arsenical preparations in adequate dosages cause the disappearance of signs of gummatous activity in from one to seven days, according to Hahn. He further remarks that "The therapeutic test may be adjudged to be definitely positive only if there is striking change in objective manifestations in direct temporal relationship to antisyphilitic treatment, and *if such change is maintained over a long observation period measured in months, or, preferably, in years.*"

In both the cases reported in this paper, there was clinical evidence of an active gummatous process and definite fulfilment of the criteria of the therapeutic test. In case 2 biopsy further substantiated the diagnosis.

The total doses of penicillin employed were 920,000 and 3,200,000 Oxford units. In the first case dramatic results were obtained following an initial course of only 320,000 units. That visceral gummas should respond to this antibiotic substance is to be expected in the light of recent work on benign late syphilitic lesions in locations accessible to inspection.[2] Observations extending over six hundred and eighty-six

1. Hahn, R. D.: Syphilis of the Liver, Am. J. Syph., Gonor. & Ven. Dis. **27**:529-562 (Sept.) 1943.

2. Dexter, D. D., and Tucker, H. A.: Penicillin Treatment of Benign Late Syphilis: A Report of Twenty-One Cases, Am. J. Syph., Gonor. & Ven. Dis. **30**: 211-226 (May) 1946.

and four hundred and ninety-one days in the 2 cases reported in this paper have not disclosed evidence of relapse, except for a rise of the serum flocculation titer in each. These data suggest that penicillin is at least as effective in the treatment of visceral gummas as the other forms of antisyphilitic treatment and offers the additional advantage of almost complete lack of toxicity, a factor of some importance when disease of the liver is present.[3]

The response of the osseous lesions in case 1 was satisfactory from the standpoint of immediate relief of symptoms, and the roentgenographic evidence of resolution of the proliferative process was convincing. Serum alkaline phosphatase activity fell as proliferative activity declined. Skeletal abnormalities were not demonstrated in case 2, however, and no adequate explanation for the increased alkaline phosphatase activity is forthcoming.

From the laboratory standpoint it is noteworthy that the results of spinal fluid tests became negative after the administration of penicillin; the results of blood serologic tests were less affected. Each patient had hyperproteinemia with an absolute increase in the globulin fraction; sustained reversal of the albumin-globulin ratio to normal was demonstrated in each. Other laboratory findings, such as the hemoglobin content, and erythrocyte determinations likewise paralleled the general clinical improvement.

SUMMARY

Acquired benign late syphilis (gummas) of the liver and osseous system (case 1) and multiple hepatic gummas due to congenital syphilis (case 2) were diagnosed clinically. Both diagnoses were substantiated by therapeutic tests and the second also by biopsy.

The patients received 920,000 and 3,200,000 Oxford units, respectively, of commercial sodium penicillin intramuscularly, with dramatic alleviation of acute symptoms and sustained objective and subjective improvement over observation periods of six hundred and eighty-six and four hundred and ninety-one days.

These results show that visceral gummas heal under treatment with commercial penicillin mixtures at least as well as they do under other forms of antisyphilitic treatment. The apparently nontoxic properties of penicillin recommend it particularly in cases in which disease of the liver is present.

3. Moore, J. E.: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 304.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1944 to June 1945

WALTER LINCOLN PALMER, M.D.

WILLIAM E. RICKETTS, M.D.
AND
SAMUEL N. MAIMON, M.D.
CHICAGO

(Concluded from Page 250)

DUODENUM

Congenital Anomalies.—Sumner and Morris [217] report a case in which duodenal atresia in a newborn infant, diagnosed early, was successfully treated by duodenojejunostomy. In Mosquera's [218] case the atresia proved fatal at the age of 18 months.

Secretion.—Comfort [219] reviews the literature of the last thirty years on duodenal content in health and disease and reaches the following conclusions: During fasting the duodenal content of healthy subjects with achlorhydria is alkaline; in those with acid-secreting stomachs it is acid both in the fasting state and after meals; the reaction of the duodenal content of healthy subjects varies roughly with the amount of acid entering the duodenum; the acidity does not vary greatly between the first and the second portion; drugs, such as atropine sulfate, morphine and the sodium salt of dehydrocholic acid, increase the average p_H of the duodenal content; the antacids used in the treatment of peptic ulcer increase it temporarily; the content of the duodenum in patients with duodenal ulcer is more acid than the normal, the p_H averaging about 2 points lower. Purified secretin evoked secretion of a greater volume of pancreatic juice containing a greater volume of amylase, trypsin and lipase in patients with duodenal ulcer than in normal persons. The secretion of bicarbonate was approximately equal in the two groups.[220]

217. Sumner, W. C., and Morris, K. A.: Duodenal Atresia in the Newborn: Case Report, Am. J. Surg. **68**:120-123, 1945.

218. Mosquera, J. E.: Anomalia Intestinal, Semana méd. **51**:1025-1027, 1944.

219. Comfort, M. W.: Acidity of the Duodenal Contents in Health and Disease: A Review of Clinical Investigations, Gastroenterology **4**:135-146, 1945.

220. Comfort, M. W., and Osterberg, A. E.: External Pancreatic Secretion in Cases of Duodenal Ulcer, Gastroenterology **4**:85-91, 1945.

The interdigestive discharge of duodenal content is considered by Berger and Oppenheim [221] to be a cyclic physiologic phenomenon found in so-called resting organs.

Block, Portis and Necheles [222] studied the effect of twenty different detergents on trypsin and found that the inhibitory effect is diminished or abolished by certain substances, such as cream, butter, lecithin, glycerin esters or fatty acids and particularly triacetin.

Injury.—Operation was required to remove a bobbie pin from the duodenum of a 13 month old child.[223] Trafford [224] reports a retroperitoneal rupture of the duodenum, the mechanism of which was uncertain.

Perforation of the third portion of the duodenum by an atherosclerotic abdominal aorta without aneurysm is reported. The condition is rare, having been described only twice before.[225]

Ulcer of the Second Portion.—Crymble [226] reports 4 cases. In 2 of them the lesion was diagnosed only at operation. Weinberger and Rosenthal [227] report a choledochoduodenal fistula due to a duodenal ulcer that penetrated into the common bile duct. The biliary system was well visualized roentgenologically after oral administration of barium sulfate.

Tuberculous Adenitis.—Two instances of duodenal obstruction resulting from tuberculous adenitis have been described.[228]

Carcinoma.—There are reported 2 cases of carcinoma of the suprapapillary portion of the duodenum, 1 of the third portion, and 1 case of primary carcinoma of the liver with a spontaneous cholecystoduodenal fistula.[229]

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221. Berger, W. V., and Oppenheim, E.: The Interdigestive Discharge of Duodenal Content: I. The Rate of Discharge; Four Rhythms, Gastroenterology **4**:228-242, 1945.

222. Block, C. L.; Portis, S. A., and Necheles, H.: The Effect of Detergents on the Proteolytic Activity of Trypsin, Gasteroenterology **1**:45-50, 1944.

223. Latraverse, V., and Ricard, P. M.: Duodenoscopic Removal of a Bobbie-Pin Through a Gastrotomy in a Child Thirteen Months Old, Canad. M. A. J. **51**: 560-562, 1944.

224. Trafford, P. A.: Traumatic Retroperitoneal Rupture of the Duodenum, Lancet **2**:145-146, 1944.

225. Bernstein, B. M.; Slater, S. R., and Grayzel, D. M.: Perforation of the Aorta into the Alimentary Tract: Case Report, Clinics **3**:447-449, 1944.

226. Crymble, P. T.: Ulcer of the Second Part of the Duodenum, Brit. J. Surg. **32**:500-502, 1945.

227. Weinberger, J., and Rosenthal, A.: Choledochoduodenal Fistula: Case Report, Am. J. Roentgenol. **53**:470-473, 1945.

228. Marshak, R. H., and Dreiling, D.: Duodenal Obstruction Due to Tuberculous Lymphadenitis, Radiology **44**:495-497, 1945. Ruiz, M.: Estenosis duodenal profunda por ganglios mesentéricos tuberculosos, siendo este el foco Primario, Medicina, Madrid (pt. II.) **12**:775-780, 1944.

(Footnotes continued on next page)

In Cattell's [230] experience carcinoma of the ampulla of Vater is more common and less malignant than that of the pancreas. In 18 patients pancreatoduodenal resection was carried out, with 3 deaths (17 per cent). Satisfactory results were obtained in 13. Of these 1 has been well two years, 5 are alive after eighteen months, 4 after one year and 3 are in good condition during the current year of operation.

SMALL INTESTINE (DUODENUM, JEJUNUM, ILEUM)

Review.—Kiefer's [231] review of fifty-five current papers on diseases of the small intestine is excellent.

Anatomy and Anomalies.—Herstone and Freund [232] in a study of 54 cadavers conclude that there is no anatomic basis for estimating the distance of a small intestinal lesion from the duodenojejunal junction by its position in the peritoneal cavity; the normal variations are too great.

Bremer [233] reviews the literature and the theories of the development of diverticula and duplications of the intestinal tract. In the development of the intestinal tube, proliferation of the inner epithelial layer may produce occlusion of the lumen in the fifth week of embryonal life, but usually complete canalization occurs by the twelfth week. Thorlakson [234] describes a congenital valve of the upper part of the jejunum which was probably due to incomplete disappearance of this embryonal epithelial tissue in a 3 year old child with incomplete intestinal obstruction. Erb and Smith [235] report 2 cases of atresia of the intestine, multiple in type in one and single in the other. A premature infant with congenital atresia of the ileum, intestinal perforation and peritonitis is reported on together with a 23 month old boy with a five day history of obstruction who was found to have double intussusception

229. Cohn, I.: Carcinoma of the Duodenum: Report of Two Cases in Suprapapillary Portion, Tr. South. S. A. (1943) **55**:54-62, 1944. Shallow, T. A.; Eger, S. A., and Carty, J. B.: Primary Carcinoma of Third Portion of Duodenum, Surgery **16**:939-946, 1944. Pomeranz, R.; Grady, H. G.; Peelen, M., and Magnes, M.: Spontaneous Cholecystoduodenal Fistula in a Patient with a Primary Hepatoma of the Liver, Radiology **43**:582-587, 1944.

230. Cattell, R. B.: Pancreatoduodenal Resection: A Preliminary Report of Eighteen Cases, New England J. Med. **232**:521-526, 1945.

231. Kiefer, E. D.: The Small Intestine: A Review of Current Literature, Gastroenterology **3**:388-398, 1944.

232. Herstone, S. T., and Freund, S.: The Normal Distribution of the Small Intestine, Am. J. Roentgenol. **52**:46-51, 1944.

233. Bremer, J. L.: Diverticula and Duplications of the Intestinal Tract, Arch. Path. **38**:132-140 (Sept.) 1944.

234. Thorlakson, P. H. T.: Report on a Case of Congenital Valvular Obstruction of the Upper Jejunum, Manitoba M. Rev. **24**:354, 1944.

235. Erb, W. H., and Smith, D. C.: Atresia of Small Intestine: Two Case Reports: One Multiple Atresia with Survival, Ann. Surg. **120**:66-72, 1944.

of the bowel.[236] A successful operation in 1 newborn infant with congenital ileal atresia, gangrene, perforation and peritonitis is described.[237]

Haxton [238] reports the death of a newborn infant with a congenital anomaly consisting of a grossly distended and congested small bowel ending in a piriform sac. There was no mesenteric fixation to the posterior abdominal wall; the intestine was twisted around a peritoneal fold enclosing the superior mesenteric artery.

Five fatal cases of volvulus in the newborn arising because of congenital defects in the development of the midgut are presented by Buckley and Wells.[239] Steward [240] described 2 instances of faulty third stage rotation.

Physiologic Aspects.—In a study of the nervous mechanisms of the muscularis mucosae, King and Robinson [241] conclude that: 1. The muscularis mucosae of the small and large intestine of the dog is innervated by both cholinergic and adrenergic motor nerves. 2. Meissner's plexus contains ganglion cells the endings of which are cholinergic, also cells with adrenergic endings. 3. No conclusive evidence has been obtained for the presence of an inhibitory neural mechanism of the muscularis mucosae. 4. The rhythmic movements of the muscularis mucosae are basically myogenic but can be initiated or augmented through the nervous mechanism. 5. The muscularis mucosae may play an important mechanical role not directly connected with the processes of secretion and absorption.

Youmans,[242] studying the intestinointestinal inhibitory reflex, found that the stimulus by which intestinal motility is inhibited on distention of the bowel is mediated through a long reflex arc involving the dorsal and lumbar segments of the spinal cord. There was no evidence that the vagus nerves contain either afferent or efferent pathways for the

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236. Ficarra, B. J., and Degen, W. B.: Congenital Atresia of the Ileum, Spontaneous Perforation and Multiple Intussusception, Am. J. Surg. **65**:123-126, 1944.

237. Arnheim, E. E.: Congenital Ileal Atresia with Gangrene, Perforation and Peritonitis in a Newborn Infant: Staged Operations; Obstructive Resection, Ileocolostomy and Excision of Exteriorized Ileum, Am. J. Dis. Child. **69**:108-116 (Feb.) 1945.

238. Haxton, H.: Congenital Absence of Continuity Between Small and Large Intestine, with Abnormal Blood-Supply of the Proximal Colon, Brit. J. Surg. **32**:540, 1945.

239. Buckley, R. P., and Wells, A. H.: Volvulus in the Newborn, with a Report of Five Fatal Cases, Minnesota Med. **27**:916-919, 1944.

240. Steward, J. A.: Faulty Intestinal Rotation: Case Reports, Am. J. Surg. **65**:425-429, 1944.

241. King, C. E., and Robinson, M. H.: The Nervous Mechanisms of the Muscularis Mucosae, Am. J. Physiol. **143**:325-335, 1945.

242. Youmans, W. B.: The Intestino-Intestinal Inhibitory Reflex, Gastroenterology **3**:114-118, 1944.

reflex. Crohn, Olson and Necheles [243] found that anesthetic drugs applied topically to the mucosa inhibit intestinal motility and tone but not gastric motility.

Preoperative administration of usual doses of morphine and scopolamine inhibited motility of the small bowel in 11 patients. Under these conditions spinal anesthesia did not stimulate the small bowel to contract against a mild distending force (balloon of a Miller-Abbott tube).[244]

Van Liere and his associates [245] noted that in dogs premedicated with cocaine and then subjected either to simple anoxia or to anemic anoxia there was a statistically significant decrease in the propulsive motility of the small intestine.

McGee and Hastings [246] confirmed the relative hypotonicity of certain specimens obtained from the fasting human jejunum by intubation, but found that later specimens were isotonic, suggesting that the hypotonicity of the initial specimens is attributable to the admixture of saliva and other hypotonic solutions occasioned by the intubation procedure.

Hormones.—The gastrointestinal mucosa produces nine endocrine principles. The existence of eight of these is unchallenged, although they do not seem vital for the maintenance of life. The following hormones have been identified by physiologic methods: secretin, cholecystokinin and enterogastrone. Enterogastrone has three components; one inhibits gastric secretion, a second inhibits the motility of the vagotomized stomach and a stird inhibits the motility of the normally innervated stomach.

The existence of gastrin, enterocrinin and pancreozymin has been established by physiologic methods, but the results of the physiologic investigation lack adequate confirmation. Gastrin stimulates gastric juice in a histamine-like manner, while enterocrinin stimulates the secretion of intestinal juice. The existence of villikinin and enterocrinin require confirmation. The former is supposed to stimulate the movements of the villi, while the latter stimulates the motility of the intestine.[247]

243. Crohn, N.; Olson, W. H., and Necheles, H.: The Local Effect of Topic Anesthetic Drugs on the Motility of the Gastrointestinal Tract of the Human and the Dog, Surg., Gynec. & Obst. **79**:41-49, 1944.

244. Helm, J. D., and Ingelfinger, F. J.: The Effect of Spinal Anesthesia on the Motility of the Small Intestine, Surg., Gynec. & Obst. **79**:553-556, 1944.

245. Van Liere, E. J.; Northup, D. W., and Stickney, J. C.: The Effect of Anoxia and Anemic Anoxia on the Motility of the Small Intestine and the Influence of an Epinephrine-Potentiating Agent, Am. J. Physiol. **142**:615-620, 1944.

246. McGee, L. C., and Hastings, A. B.: The Osmotic Pressure of Fasting Jejunal Secretions in Man, Gastroenterology **4**:243-250, 1945.

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Physiologic Effects of Massive Resection.—Prioleau [248] reports 2 cases of massive resection of the small intestine. One of the patients with a resection of 260 cm. of small intestine and 31 cm. of sigmoid, finally regained an excellent state of health; the other survived the resection of 354 cm. of small intestine and 40 cm. of sigmoid but died four months later of nutritional disturbances and postoperative complications. In the first case approximately 40 per cent of the small bowel was removed; in the second, about 53 per cent—again illustrating the fact that a resection of more than 50 per cent of the small intestine is incompatible with life. In Holman's [249] case of obstruction due to volvulus with mesenteric thrombosis, 20 feet (6 meters) of gangrenous bowel, including 19 feet (5.5 meters) of small bowel, ileum, cecum and ascending colon, was resected, and the patient recovered. The stools were semiformed and slightly pale, and contained a moderate excess of unsplit neutral fat, but not an excess of split fat, and only a few undigested muscle fibers. Elman and Read [250] report regional ileitis necessitating removal of all the small intestine except for 3 feet (91.5 cm.) of jejunum just distal to the ligament of Treitz, and also the right half of the colon. The patient gained 50 pounds (22.5 Kg.) of weight and experienced normal bowel function on an unrestricted diet. Cosh [251] describes thrombosis of the superior mesenteric artery requiring resection of the entire ileum, the lower part of the jejunum and the cecum. The patient survived for one year in spite of intractable diarrhea, vomiting, cramps in the legs and the arms and, finally, tetany with low blood calcium (7.2 mg. per hundred cubic centimeters).

Intubation.—In an excellent paper Miller [252] outlines his extensive experience with intestinal intubation, emphasizing the value of this procedure for the study of nutritional problems, drug effects and pathologic function of the intestine. Using the Alnico tip in a Miller-Abbott tube, Mayer was able to pass the tube from the stomach to the duodenum in one to two minutes by guiding the highly magnetic tip through the pylorus with an electromagnet.[253]

247. Ivy, A. C.: The Gastrointestinal Hormones: Their Physiology and Applications, Tr. & Stud., Coll. Physicians, Philadelphia **12**:101-107, 1944.

248. Prioleau, W. H.: Massive Resection of the Small Intestine: Report of Two Cases, Tr. South. S. A. (1943) **55**:84-88, 1944.

249. Holman, C. C.: Survival After Removal of Twenty Feet of Intestine, Lancet **2**:597-598, 1944.

250. Elman, R., and Read, J. A.: Nutritional Recovery Following Removal of All but Three Feet of Jejunum and Half of the Colon, J. Missouri M. A. **42**:145-146, 1945.

251. Cosh, J. A.: Tetany After Extensive Gut Resection, Lancet **2**:596-597, 1944.

252. Miller, T. G.: Intubation Studies of the Human Small Intestine: XXIV. A Review of a Ten Year Experience, Gastroenterology **3**:141-154, 1944.

253. Mayer, H., Jr.: Passage of Miller-Abbott Tube Through Pylorus with Aid of Electromagnet, U. S. Nav. M. Bull. **43**:463-466, 1944.

Davis and Hansen [254] found that by using the Wangensteen aspiration immediately after operation they decreased the number of days of distention of the abdomen and gas pains. Swallowed air is thought to be the main source of the gas.

Roentgenographic Appearance.—Of 73 patients whose small intestines were studied by Ruffin and his associates,[255] 28 of them had normal small intestines; a "deficiency pattern" was detected in the remainder, mild in 12, moderate in 23 and severe in 10. Definite alterations of pattern of the small intestine were common in patients with sprue and frank vitamin B complex deficiency but were present also in apparently normal persons. This work is particularly important because of the demonstration that the so-called deficiency pattern may occur in apparently normal persons who show no laboratory evidence of a deficiency state and the consequent conclusion that minor changes of the pattern of the small intestine should be interpreted with caution.

Volvulus.—Barbosa [256] reports that a 20 year old woman with volvulus of the entire small bowel was operated on successfully.

Intussusception.—Several instances of intussusception have been reported: One patient was a 14 year old boy [257]; a second, a 13 year old girl, who was found at operation to have a small adenocarcinoma of the ileum with intussusception [258]; in 2 patients a submucosal lipoma of the ileum served as the leader [259]; in another, a jejunal polyp [260]; in still another, a Meckel's diverticulum [261]; 2 patients—father and daughter—had intussusception of the small bowel caused by adenocarcinoma and occurring alike in each [262]; in 2 patients jejunal intussusception developed through a gastroenterostomy stoma,[263] in one of them retrogradely through a subtotal gastrectomy stoma.[264]

254. Davis, H. H., and Hansen, T. M.: Investigation of the Cause and Prevention of Gas Pains Following Abdominal Operation, Surgery **17**:492-497, 1945.

255. Ruffin, J. M.; Baylin, G. J., and Cayer, D.: The Clinical Significance of Alteration of the Small Intestine Pattern as Demonstrated by X-Ray, Gastroenterology **4**:289-295, 1945.

256. de Castro Barbosa, J. J.: Volvulus of the Entire Small Intestine and Its Mesentery: Case Report, Am. J. Surg. **64**:400-404, 1944.

257. Cabot Case 31021, New England J. Med. **232**:49-52, 1945.

258. Puppel, I. D., and Morris, L. E., Jr.: Adenocarcinoma of the Ileum in a Girl of Thirteen, Am. J. Surg. **66**:113-115, 1944.

259. Cabot Case 31041, New England J. Med. **232**:113-115, 1945; Cabot Case 31131, ibid. **232**:350-353, 1945.

260. Copello, O., and Etala, E.: Polipo de yeyuno: Invaginación intestinal Recidivante, Prensa méd. argent. **31**:2153-2154, 1944.

261. Smith, R.: Volvulus of the Small Intestine due to a Meckel's Diverticulum. Brit. J. Surg. **32**:510-511, 1945.

262. Foster, D. B. E.: Adenocarcinoma of the Small Intestine in Father and Daughter, Brit. M. J. **2**:78-79, 1944.

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Herniation and Strangulation.—Goode and Newbern [265] report intestinal obstruction due to strangulation of the bowel, which had thrust through a defect in the broad ligament of the uterus. Fatal strangulation of the jejunum occurred when the bowel prolapsed through a genuine aperture of the great omentum.[266] An interstitial ventral hernia with distended loops of bowel was detected roentgenologically.[267]

Mesenteric Vascular Occlusion.—Ficarra [268] reports 15 cases of mesenteric vascular occlusion, in 3 of which the condition was treated successfully by intestinal resection. The high mortality (60 to 90 per cent) is attributed to shock.

Foreign Bodies: Obstruction and Perforation.—Ingested foreign bodies can be broadly graded, according to McKechnie,[269] into metallic bodies, bones and wood splinters. In 90 cases of foreign body in which the site of perforation was recorded, the break-through occurred in the ileocecal region in 63, including 10 with perforation of Meckel's diverticulum, 10 with perforation of the lower part of the ileum, 10 with perforation of the cecum and 33 with perforation of the appendix. In only 5 cases did perforation occur in the gastroduodenojejunal region. Perforation occurred in the colon in 15, in the hepatic flexure in 3, in the transverse colon in 1, in the splenic flexure in 2, in the descending colon in 1, in the sigmoid in 5, in the rectum in 3. In 7 cases no perforation was found but foreign bodies were in abscesses and various abdominal recesses. A nail swallowed accidentally perforated through the rectum into the perineum and the bladder three days later. Hurwich [270] found that in 73 per cent of cases of foreign body perforation occurs about the ileocecal region. In an instance of a toothpick lodged in the right colic gutter, the patient could not recall having swallowed the toothpick.

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263. Butler, F. E.; Woolley, I. M., and Burton, W. Y.: Jejunal Intussusception Through a Gastro-Enterostomy Stoma, Radiology **44**:498, 1945.

264. McNamara, W. L.: Retrograde Jejunogastric Intussusception Through a Subtotal Gastrectomy Stoma, Ann. Surg. **120**:207-210, 1944.

265. Goode, T. V., and Newbern, W. R.: Intestinal Obstruction Associated with Defects in the Broad Ligaments of the Uterus: Review of Literature and Case Report, Am. J. Surg. **65**:127-132, 1944.

266. Sanes, S., and Postoloff, A. V.: Strangulation of the Small Intestine Due to Prolapse Through an Aperture in the Great Omentum, Gastroenterology **3**:30-32, 1944.

267. Gray, W., and Horwitz, M.: Interstitial Ventral Hernia Involving the Small Intestine, Am. J. Surg. **66**: 134-135, 1944.

268. Ficarra, B. J.: Mesenteric Vascular Occlusion: A Presentation of Fifteen Cases, Am. J. Surg. **66**: 168-177, 1944.

269. McKechnie, W. R.: Perforation of the Intestine by a Swallowed Sharp Foreign Body, Australian & New Zealand J. Surg. **13**:265-266, 1944.

270. Hurwich, J. J.: Perforation of the Caecum by a Toothpick, M. Bull. Vet. Admin. **21**: 232-233, 1944.

Radley [271] describes an instance of intestinal obstruction produced when a gallstone which had ulcerated through the gallbladder into the duodenum was arrested in the lower part of the ileum.

Hunt and Bowden [272] emphasize that the signs and symptoms are minimal when rupture of the intestine results from nonpenetrating injuries of the abdominal wall. The picture is primarily that of slowly developing generalized peritonitis. In the 5 cases reported the mortality rate was 40 per cent. Similarly in 5 cases in which the ruptured bowel was subjected to operation by Bunch [273] there were 2 deaths.

Telford [274] observes that while the mortality from gunshot wounds of the abdomen was 90 per cent in the Civil War, it was still 50 per cent in the recent conflict. In 146 cases of perforating abdominal injuries described by Sloan [275] the mortality was 22.6 per cent for the entire group. After the introducion of frequent transfusions and treatment with sulfonamide compounds the rate dropped to 10.1 per cent. Experimental support for the use of sulfonamide compounds is provided by Sarnoff and Poth.[276] In an experiment carried out with 15 mongrel dogs, ligation of the venous return from segments of the ileum 50 cm. in length in 8 control animals was always lethal, death occurring from peritonitis in forty-eight hours, whereas, of the 7 dogs similarly operated on but treated with 0.5 Gm. of succinylsulfathiazole per kilogram of body weight per day for ten days before operation, 70 per cent survived indefinitely.

Aneurysm.—Levine and Valk [277] report a gastrointestinal hemorrhage in an 18 year old girl which was found at operation to be the result of rupture of an aneurysm of a submucosal vessel in the jejunum.

Diverticula.—Johnson [278] describes an instance of multiple diverticula of the first part of the jejunum. One hundred and eighty-seven such

271. Radley, S. B.: Intestinal Obstruction Due to a Gall Stone, Clin. J. **73**: 226-227, 1944.

272. Hunt, G. H., and Bowden, J. N.: Rupture of Intestine Caused by Nonpenetrating Trauma of the Abdominal Wall: A Report of Cases, Arch. Surg. **49**: 321-326 (Nov.) 1944.

273. Bunch, J. R.: Intestinal Perforations Due to Non-Penetrating Abdominal Trauma, South. M. J. **37**:717-722, 1944.

274. Telford, D.: Gunshot Wounds of the Abdomen (with Report of a Case), Canad. M. A. J. **52**:38-42, 1945.

275. Sloan, H. E.: Perforating Abdominal Injuries, with Special Reference to Reduction in Mortality by the Use of Transfusions and Sulfonamides, Surg., Gynec. & Obst. **79**: 337-341, 1944.

276. Sarnoff, S. J., and Poth. E. J.: I. The Protective Action of Succinylsulfathiazole Following Simple Venous Occlusion, Surgery **16**: 927-931, 1944.

277. Levine, J., and Valk, A. de T.: Aneurysm with Rupture of a Submucosal Artery in the Jejunum: Case Report, Am. J. Clin. Path. **14**: 586-589, 1944.

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cases are reported in the literature. Walker [279] discusses the complications.

Meckel's Diverticulum.—Sibley [280] in an excellent paper on Meckel's diverticulum estimates its incidence as about 4 per cent in newborn infants and 1 to 3 per cent in adults. In addition to cysts, fecal fistulas and the intestine prolapsed through the umbilicus, the common signs and symptoms may be divided into the obstructive, the inflammatory and the peptic ulcer type. One of the chief purposes of the paper is to call attention to the frequency with which diverticula containing heterotopic gastric mucosa may produce not only the pain and the bleeding of peptic ulcer but a syndrome somewhat akin to diverticulitis. No inflammation is present. Sibley labels the condition as dyspepsia Meckeli and attributes it to spasm of the bowel resulting from irritation produced by the acid and pepsin.

Of 8 specimens studied by Troll,[281] 3 contained pancreatic tissue and 6 gastric mucosa; 1 contained both types.

Mottram and Garland [282] were able to make a roentgenologic diagnosis of Meckel's diverticulum by means of the retained barium sulfate in 1 case.

Gendel and Beaver [283] report the unique case of a 20 year old soldier with Meckel's diverticulum who had acute appendicitis and nevertheless made an uneventful postoperative recovery.

Regional Ileitis.—Kiefer [284] found that regional ileitis occurred seventy times in 100,000 registrants at the Lahey Clinic. In a group of 63 patients subjected to operation, subsequent recurrence of the disease was noted in 12.

In an excellent review Bockus [285] discusses the present status of chronic regional enteritis and presents his experience with 19 patients treated surgically; 11 were subjected to ileocolostomy, with 1 death; the remaining 10 are alive, but 50 per cent of them give evidence of

278. Johnson, J. A.: Diverticula of the Jejunum, Minnesota Med. **28**:395-396, 1945.

279. Walker, R. M.: The Complications of Acquired Diverticulosis of the Jejunum and Ileum, Brit. J. Surg. **32**:457-463, 1945.

280. Sibley, W. L.: Meckel's Diverticulum: Dyspepsia Meckeli from Heterotopic Gastric Mucosa, Arch. Surg. **49**:156-166 (Sept.) 1944.

281. Troll, M. M.: Aberrant Pancreatic and Gastric Tissue in the Intestinal Tract, Arch. Path. **38**:375-380 (Dec.) 1944.

282. Mottram, M. E., and Garland, L. H.: Meckels Diverticulum, Am. J Roentgenol. **53**:142-146, 1945.

283. Gendel, S., and Beaver, M. G.: An Unusual Case of Meckel's Diverticulum, Ann. Surg. **121**:981-983, 1945.

284. Kiefer, E. D.: Regional Ileitis, Clinics **3**:506-515, 1944.

285. Bockus, H. L.: Present Status of Chronic Regional or Cicatrizing Enteritis, J. A. M. A. **127**:449-456 (Feb. 24) 1945.

recurrence of the stenotic process. Two additional patients underwent resection with anastomosis of normal ileum; a third, with extensive segmental ileitis, was subjected to resection of approximately 5 feet (1.5 meter) of the terminal part of the ileum and the ascending colon followed by ileotransversostomy. Thus of 14 patients subjected to operation, 1 died, and 8 (62 per cent) showed recurrent disease. In 5 cases of ileocolitis, ileosigmoidostomy was carried out with a mortality of 40 per cent—two deaths. One patient died three and three-quarters years later; 2 are alive, four and eight years afterward. In summary, then, of 19 patients subjected to operation, good results were obtained only in 7.

Schepers [286] divides the lesion into two components: a primary phase, characterized by (*a*) a stage of edema of the submucosa and the serosa with dilatation of submucosal lymphatics and hyperemia of juxtamuscular adventitial blood vessels, (*b*) a stage of plasma cell infiltration of submucosa and serosa, (*c*) diffuse fibrosis with disappearance of plasma cells except where trapped and (*d*) healing; a secondary phase, characterized by ulceration, which may be superimposed on any primary phase with corresponding modification of the pathologic process. There are tendencies leading to early or late perforation, fistulation and granuloma formation. The importance of a "neuropathic disturbance" of the myenteric plexuses or of the mesenteric and celiac ganglions is stressed with the suggestion that the original neuropathic lesion is possibly a type of visceral herpes zoster.

Ebrill [287] reports a 9 year old girl who underwent a 6 inch (15 cm.) resection of the bowel with recovery. Spellberg and Gray [288] describe a 23 year old soldier whose disease was confined to the proximal part of the jejunum and required resection of 12 inches (30.5 cm.) of bowel. The symptoms began two months after a nonpenetrating injury of the abdomen. In a 30 year old Negress described by Rees,[289] the proximal part of the jejunum was involved, and complete obstruction was produced at three isolated places.

With regard to treatment, Crohn [290] remarks that "my approach to this disease is more and more conservative." The upper part of the intestine, if involved, shows a tendency to heal itself, in contrast with

286. Schepers, G. W. H.: The Pathology of Regional Ileitis, Am. J. Digest. Dis. **12**:97-116, 1945.

287. Ebrill, D.: A Case of Regional Enteritis in Childhood, Brit. J. Surg. **32**:512-514, 1945.

288. Spellberg, M. A., and Gray, L. W.: Regional Enteritis of the Proximal Jejunum Following Trauma, Surgery **17**:343-350, 1945.

289. Rees, V. L.: Regional Jejunitis: Report of an Unusual Case, Am. J. Surg. **67**:119-122, 1945.

290. Crohn, B. B.: V. The Use of Sulfonamides in Ileitis, Gastroenterology **4**:11-13, 1945.

the terminal part of the ileum where the changes progress to scar formation and eventually to obstruction. Succinylsulfathiazole has proved helpful before and after operation.

Tuberculosis.—Camiel [291] in a well illustrated paper discusses the direct roentgenographic manifestations of ileocecal tuberculosis. The presence of active pulmonary tuberculosis greatly simplifies the diagnostic problem, especially when the terminal part of the ileum is the only portion of the bowel affected. Richieri [292] likewise gives a well illustrated discussion of the disease, and Paul [293] reports 5 cases of stricture, tuberculous in origin in 4 of them and due to regional enteritis in 1.

An unusual case of chronic bleeding from the gastrointestinal tract was attributed at operation to lesions of the small intestine. The pathologist was puzzled by the gross and microscopic pictures, considering tuberculosis and regional enteritis in the differential diagnosis. A guinea pig inoculated revealed tuberculosis.[294]

Sarcoid.—Watson and his colleagues [295] describe two very interesting lesions of the small intestine and mesenteric lymph nodes clinically resembling ileojejunitis or Crohn's disease. The roentgen picture was striking with multiple polyposis-like small defects in the pattern of the mucous membrane. Resection of the affected segments produced marked improvement in each instance. Histologic study showed the widespread epithelioid cell tubercle formation typical of sarcoidosis. No evidence of sarcoid was noted elsewhere. Reexamination of the pathologic material from 21 other cases of regional ileitis failed to demonstrate such lesions. Hence the authors conclude that the two described represent isolated sarcoidosis of the small intestine.

Sprue.—Andersen [296] found the Sperry method of determining fecal fat to be the most reliable. A comparison of the chemical and the microscopic method showed a high degree of correlation, indicating that the latter method may be useful for screening outpatients. The daily determination of total fecal fat gives a more accurate picture of

291. Camiel, M. R.: Ileocecal Tuberculosis, Radiology **44**:344-351, 1945

292. Richieri, A.: Tuberculosis intestinal: su tratamiento, Prensa méd. Argent. **31**:1647-1658, 1944.

293. Paul, M.: Stenosis of the Small Intestine from the Cicatrization of Isolated Inflammatory Lesions, Brit. J. Surg. **32**:371-376, 1945.

294. Cabot Case 30321, New England J. Med. **231**:237-242, 1944.

295. Watson, C. J.; Rigler, L. G.; Wangensteen, O. H., and McCartney, J. S.: Isolated Sarcoidosis of the Small Intestine Simulating Non-Specific Ileo-Jejunitis, Gastroenterology **4**:30-52, 1945.

296. Andersen, D. H.: Celiac Syndrome: I. Determination of Fat in Feces; Reliability of Two Chemical Methods and of Microscopic Estimate; Excretion of Feces and of Fecal Fat in Normal Children, Am. J. Dis. Child. **69**:141-151 (March) 1945.

the fat disturbance in digestion than does that of the neutral fat alone. In a study of the fecal fat of infants and children with congenital pancreatic deficiency Andersen [297] found that the amount of fecal fat was decreased when the amount of dietary fat was reduced, the decrease of output being roughly proportional to the decrease of intake. The effect of pancreatin was variable, although the excretion of fat was usually reduced. Andersen concluded that the inefficiency of protein digestion, as well as that of fat digestion, has been inadequately stressed heretofore. An optimal diet for patients with congenital pancreatic insufficiency is suggested: Protein should contribute about 25 per cent of the calories; fat should be low; the carbohydrate content should be high, with starch given in part as cereal and potato if these foods are tolerated clinically. Diamond [298] gives a good discussion of chronic diarrhea in children, with considerable attention to pancreatic fibrosis and celiac disease.

Klein and Porter [299] describe a 16 year old boy with constant hypoproteinemia, hypocalcemia, flat dextrose tolerance curve and slight, although definite, steatorrhea who was studied for four years. At autopsy these abnormalities were found to be due to tuberculosis of the mesenteric and retroperitoneal lymph nodes. Howat [300] discusses the occurrence of a spruelike syndrome characterized by stomatitis and steatorrhea which develops occasionally in the course of dysentery. He suggests that it may be a manifestation of a specific deficiency of the vitamin B complex. A syndrome resembling sprue developed in a patient with intrahepatic jaundice following treatment with oxophenarsine hydrochloride. Recovery occurred.[301]

Benign Tumors.—Collins [302] analyzes 18 cases of neurofibroma of the small intestine reported since 1929 and adds 1 case. Hanno and Mensh [303] report a fatal hemorrhage of leiomyoma of the jejunum;

297. Andersen, D. H.: Celiac Syndrome: II. Fecal Excretion in Congenital Pancreatic Deficiency at Various Ages and with Various Diets, with Discussion of the Optimal Diet, Am. J. Dis. Child. **69**:221-230 (April) 1945.

298. Diamond, L. K.: Chronic Diarrhea and Its Treatment in Infancy and Childhood, M. Clin. North America **28**:1189-1209, 1944.

299. Klein, A., and Porter, W. B.: Intestinal Malabsorption Associated with Tuberculosis of Mesenteric Lymph Nodes, Arch. Int. Med. **74**:120-130 (Aug.) 1944.

300. Howat, H. T.: Fatty Diarrhea in Chronic and Relapsing Dysentery, Lancet **2**:560-561, 1944.

301. Freis, E. D., and Mater, D. A.: Intrahepatic Obstructive Jaundice Following Mapharsen, with Development of a Spruelike Syndrome, J. A. M. A. **126**:892-894 (Dec. 2) 1944.

302. Collins, J. D.: Neurofibroma of the Small Intestine, Tr. South. S. A. (1943) **55**:74-83, 1944.

303. Hanno, H. A., and Mensh, M.: Leiomyoma of the Jejunum: Intermittent Melena of Fourteen Years' Duration and Fatal Hemorrhage, Ann. Surg. **120**:199-206, 1944.

the patient had experienced twenty known episodes of bleeding over a fourteen year period. Packard [304] reports a 16 year old girl suffering for many years from anemia labeled as "secondary" who was found at operation to have a cavernous hemangioma covering roughly 5 inches (12.5 cm.) of the ileum about 14 inches (35.5 cm.) above the cecum.

Carcinoid Tumors.—Ritchie and Stafford [305] review the literature on argentaffin tumors and report 11 cases in which the incidence of metastases was 27.2 per cent. Additional cases have been noted.[306] Esposito and Stout [307] report a plasmocytoma of the jejunum causing repeated intestinal hemorrhages over a period of three years. Laparotomy disclosed six constricting lesions of the small intestine with metastases in the regional lymph nodes.

Malignant Tumors.—Warren [308] describes 26 cases of primary cancer of the small intestine as recorded in the files of the Toronto General Hospital in the past sixteen years. Fraser [309] likewise, in a well illustrated paper, describes 21 cases of cancer of the small bowel, 12 of adenocarcinoma and 9 of sarcoma. At the Lahey Clinic 7 cases of cancer of the small intestine were seen in a period of seven years.[310]

In 5,000 necropsies Herbut and Manges [311] found 12 cases of melanoma. In 5 of these the cancer involved the small intestine and was metastatic. Twenty-five cases of melanoma of the small intestine were found in the literature; in 9 the growth was considered primary and in 16 metastatic. The authors suggest that in all such cases melanoma is in fact metastatic. Melanoblasts have not been demonstrated in the small bowel.

McDougal [312] describes a patient with a duodenal ulcer in whom carcinoma of the ileum developed, which was resected surgically. Nel-

304. Packard, G. B.: Hemangioma of the Intestine, Am. J. Surg. **67**:556-562, 1945.

305. Ritchie, G., and Stafford, W. T.: Argentaffin Tumors of the Gastrointestinal Tract, Arch. Path. **38**:123-127 (Sept.) 1944.

306. Blumgren, J. E.: Malignant Carcinoid Tumors of the Small Intestine: Report of Two Cases, Minnesota Med. **27**:620-623, 1944. Stevenson, W. O., and Blanchard, A. J.: Carcinoid Tumour of the Ileum with Metastases in the Mesenteric Lymph Nodes, Canad. M. A. J. **51**:259-260, 1944.

307. Esposito, J. J., and Stout, A. P.: Multiple Plasmocytoma of the Jejunum, Am. J. Roentgenol. **53**:33-39, 1945.

308. Warren, R. F.: Primary Malignant Tumours of the Small Bowel, Canad. M. A. J. **51**:450-457, 1944.

309. Fraser, K.: Malignant Tumors of the Small Intestine: A Review of the Literature and Report of Twenty-One Cases, Brit. J. Surg. **32**:479-491, 1945.

310. Ficarra, B. J., and Marshall, S. F.: Primary Carcinoma of the Jejunum, S. Clin. North America **25**:713-718, 1945.

311. Herbut, P. A., and Manges, W. E.: Melanoma of the Small Intestine, Arch. Path. **39**:22-27 (Jan.) 1945.

312. McDougal, W. J.: Carcinoma of the Small Intestine, Am. J. Surg. **66**:119-122, 1944.

son [313] adds 2 cases. Warren [314] describes a small intestinal obstruction produced by a secondary carcinoma from an unknown site. A second obstruction due to an unattached similar carcinoma occurred soon afterward, and the patient died.

A housewife had epigastric distress for one year and melena on two occasions; then acute intestinal obstruction developed. At operation cancerous lymphogranulomatosis of the jejunum and mesenteric lymph nodes was found.[315]

Borak [316] observed 5 lymphoblastic tumors in different parts of the digestive tract, and Bodenheimer,[317] a sarcoma 7 cm. in diameter in the wall of the jejunum. Cutler, Stark and Scott [318] report 5 cases of primary lymphosarcoma of the bowel, complicated by intussusception in 3; the patients were children. Radical surgical extirpation and roentgen therapy were used. The mortality was 80 per cent. Terminal lymphatic leukemia developed in 2 patients.

A lymphangioma of the jejunum resulted in severe anemia from continued loss of blood, as indicated on examination of the feces. At laparotomy the lesion was localized, and apparent cure was obtained.[319]

APPENDIX

Appendicitis.—(*a*) Etiologic Factors: Bowen,[320] reporting on obstructive appendicitis, states that a stercolith was found in 21 (55.3 per cent) of 38 cases, stenosis in 1 (2.6 per cent), kinks and bends in 4 (10.5 per cent) and spasm (no stercolith) or bend in 12 (31.5 per cent). In 40 of 117 cases of acute inflammation, fecal material was found obstructing the lumen; in 12 of the 40 gangrene was present. On the other hand, of 87 cases with no fecal material in the lumen, gangrene was present in only 20. It seems difficult, therefore, to attribute acute appendicitis to obstruction with resultant increase in intra-appendicular

313. Nelson, H.: Carcinoma of the Ileum, Minnesota Med. **28**:396-398, 1945.

314. Warren, R. F.: Small Bowel Obstruction Due to an Unattached Secondary Tumour, Canad. M. A. J. **52**:44-47, 1945.

315. Mascheroni, H. A.; Reussi, C., and Clerici, L. E.: Estenosis crónica del yeyunoileon por linfogranulomatosis intestinal, Arch. argent. de enferm. d. ap. digest. y de la nutrición **19**:466-478, 1944.

316. Borak, J.: Relationship Between the Lymphoblastic Tumor and the Digestive Tract, Am. J. Digest. Dis. **11**:241-244, 1944.

317. Bodenheimer, J. M.: Sarcoma of the Small Intestines: Case Report, Am. J. Surg. **66**:404-406, 1944.

318. Cutler, G. D.; Stark, R. B., and Scott, H. W., Jr.: Lymphosarcoma of the Bowel in Childhood, New England J. Med. **232**:665-670, 1945.

319. Puppel, I. D., and Morris, L. E., Jr.: Lymphangioma of the Jejunum, Arch. Path. **38**:410-412 (Dec.) 1944.

320. Bowen, W. H.: Obstructive Appendicitis, Brit. J. Surg. **32**:468-471, 1945.

pressure, necrosis, secondary infection, etc., in all cases; it is clear nevertheless that in many instances obstruction by a fecalith followed presumably by such a sequence of events is causal.

A large calculus in the appendix, believed to be the third on record, is reported by Pilcher.[321] Bunch [322] describes 4 instances of chronic obstruction of the appendix with retention of contents producing morbid changes known as mucoid disease of the appendix. In 2 cases there were no symptoms; in the other 2 the appendix was perforated.

(*b*) Diagnosis: Esguerra Gomez [323] reviews the shifting opinion regarding the roentgenologic diagnosis of appendical disease and concludes that there is increasing skepticism regarding the occurrence of "chronic appendicitis." Lazarus and Marks [324] report 3 cases of appendical abscess, in which symptoms were mainly referable to the urologic tract. Held [325] in discussing the differential diagnosis of peptic ulcer argues for the existence of chronic appendicular disease as a clinical entity. [The reviewers are not at all convinced by his argument.] A syndrome of somatic nerve root pain frequently confused with appendicitis is discussed by Murray.[326] Procaine hydrochloride block of the affected root relieves the pain at least temporarily. Knapp and Claps [327] report a rare instance of an inflamed appendix incarcerated in a femoral hernia. Buxton and Kurman [328] report the case of a 9 year old boy who on the twenty-eighth day after an appendectomy presented a temperature of 105 F. with coughing and expectoration of purulent bloody material. A bronchocolic fistula was demonstrated by roentgenogram. Two years later, the fistula had closed completely, and the patient was reported normal.

(*c*) Treatment: Stokes [329] found that acute appendicitis ranked rather high among the infirmities of naval personnel, but that the

321. Pilcher, L. S.: Giant Calculus of the Appendix: Report of a Case, New England J. Med. **232**:163-165, 1945.

322. Bunch, G. H.: Mucoid Disease of the Appendix, Ann. Surg. **121**:704-709, 1945.

323. Esguerra Gomez, G.: Present Value of Roentgenology in the Diagnosis of Appendicitis, Am. J. Roentgenol. **52**:624-636, 1944.

324. Lazarus, J. A., and Marks, M. S.: Urological Manifestations Associated with Chronic Appendiceal Abscess, Am. J. Surg. **68**:38-43, 1945.

325. Held, I. W.: The Differential Diagnosis of Peptic Ulcer, M. Clin. North America **29**:624-638, 1945.

326. Murray, G.: Root Neuritis Vs. Appendicitis, Canad. M. A. J. **51**:309-312, 1944.

327. Knapp, C. S., and Claps, L. V.: Appendicitis Incarcerated in a Femoral Hernia, Am. J. Surg. **64**:139-140, 1944.

328. Buxton, R., and Kurman, R. L.: Bronchocolic Fistula, Am. J. Surg. **67**:137-139, 1945.

329. Stokes, R. J.: Appendicitis in Naval Personnel: Observations on One Hundred and Nine Cases, U. S. Nav. M. Bull. **44**:786-789, 1945.

mortality was 75 per cent less than the average civilian mortality owing, presumably, to earlier operation. Fisher and Burch [330] report on 1,494 patients who were operated on for appendicitis over a four year period at the Brooke General Hospital, with 2 deaths. Of these, 645 had acute simple suppurative appendicitis, 34 acute perforative appendicitis with abscess formation, and 39 acute perforative appendicitis with generalized peritonitis—a total of 718 with acute suppurative appendicitis. Among these there were two deaths. The low mortality rate is attributed to early diagnosis, elimination of purgation and postoperative use of sulfanilamide. McPherson and Kinmonth [331] report a series of 730 cases of acute appendicitis with a mortality rate of 2.9 per cent for the whole series, 1.17 per cent for cases of simple acute appendicitis, 15.5 per cent for those complicated with peritonitis and 0.8 per cent for those with appendical masses.

Zaslow [332] in reporting 7 instances of appendical rupture and peritonitis interprets the low temperature (under 100 F. orally) on the third postoperative day and the persistent abdominal distention with or without peristalsis as indicative of a mechanical rather than a paralytic obstruction.

(*d*) Chemotherapy: Stafford, Beswick and Deeb [333] review a series of 908 perforated appendixes. During the five year period 1939 to 1944 the mortality rate for perforative appendicitis decreased from 9.2 to 3.4 per cent. This is attributed to the use of sulfonamide compounds.

Kaufman and Mersheimer [334] in a careful analysis of the factors influencing the mortality from appendectomy for acute appendicitis conclude

> . . . that many factors have contributed an important share to the reduction of our mortality. Among these is the judicious use of intravenous chlorides, plasma or blood to establish an optimum fluid balance during the pre- and postoperative period. Fluid balance should be established before as well as after operation. The routine use of the McBurney incision has contributed to the

330. Fisher, H. C., and Burch, J. C.: The Treatment of Acute Appendicitis, South. Med. J. **38**:255-260, 1944.

331. McPherson, A. G., and Kinmonth, J. B.: Acute Appendicitis and the Appendix Mass, Brit. J. Surg. **32**:365-370, 1945.

332. Zaslow, J.: Early Postoperative Mechanical Intestinal Obstruction Following the Removal of a Ruptured, Gangrenous Appendix, Am. J. Surg. **65**: 276-280, 1944.

333. Stafford, C. E.; Beswick, J., and Deeb, P. H.: Evaluation of Sulfonamides in the Treatment of Peritonitis of Appendiceal Origin: Review of Nine Hundred and Three Cases of Acute Perforative Appendicitis, Am. J. Surg. **64**: 227-234, 1944.

334. Kaufman, L. R., and Mersheimer, W. L.: Sulfonamides in Appendicitis: A Review of Four Hundred and Twelve Consecutive Cases and an Analysis of Fatalities, Am. J. Surg. **65**:393-403, 1944.

lowered mortality rate as has been emphasized by many observers. A better understanding of the rôle of oxygen and improved anesthesia technic share in the credit. Lastly, a more widespread understanding on the part of our staff of the fundamental importance of prompt and continuous intestinal decompression by the Wangensteen or Furness suction as well as efficient use of the Miller-Abbott tube are vital factors in the management of acute appendicitis except for the addition of the sulfonamides. Since then, the mortality rate has steadily been reduced so that since this study was completed a further group of over 200 consecutive patients of all types have been operated upon without a death. There is definite evidence of the great value of the local and general use of the sulfonamides in the reduction of the serious complications and mortality in the severe forms of acute appendicitis.

Ochsner and Johnston [335] compare the results obtained in the treatment of appendicitis in the years 1933 and 1943. The use of sulfonamide compounds, the administration of blood and plasma and the routine gastrointestinal decompression have changed the picture. The three complications, localized peritonitis, localized abscess and generalized peritonitis, were found to have been caused in 90 per cent of the cases in both years by the administration of laxatives. Immediate operation is advised for all patients with acute appendicitis whether the appendix is ruptured or unruptured; conservative therapy is indicated for localized inflammatory processes. The sulfonamide drugs are thought to give an added factor of safety.

Aycock and Farris [336] review 1,151 consecutive cases in which appendectomy was performed for acute appendicitis during the last decade. From 1935 to 1940, 600 cases, the mortality rate was 5.2 per cent, whereas from 1940 to 1944, 500 cases, it was 1.2 per cent. The lowering of the rate is attributed largely to the administration of sulfonamide compounds.

Kalisova [337] reports a 5 year old child with retrocecal gangrenous appendicitis. The abdomen contained "thin greenish foul-smelling fluid with gas." Hemolytic streptococci, staphylococci and gram-negative diplococci were isolated. Sodium sulfapyridine (1.0 Gm.) was injected every four hours, without demonstrable improvement. Twenty-four hours later, this was stopped, and treatment with penicillin was instituted, 15,000 units being injected into the abdominal cavity through a catheter every three hours. After the first twenty-four hours, the child began to make a striking recovery, and the gram-positive organisms seen in the abdominal fluid disappeared.

335. Ochsner, A., and Johnston, J. H.: Appendical Peritonitis, Surgery **17**: 873-892, 1945.

336. Aycock, T. B., and Farris, E. M.: Appendicitis: The Possible Effects of Sulfonamides on Mortality, Ann. Surg. **121**:710-720, 1945.

337. Kalisova, M.: Acute Appendicitis Treated with Penicillin, Brit. M. J. **2**:597, 1944.

[In the judgment of the reviewers, chemotherapy is not necessary or indeed justifiable in cases of simple acute appendicitis; when localized or general peritonitis or appendical abscess is present the use of both drugs is indicated, the sulfonamide compound being more effective against the gram-negative organisms and penicillin relatively more effective against the gram-positive ones.[338]]

In an excellent experimental study Daniel and Holbrook [339] injected a suspension of hemolytic Staphylococcus aureus among the loops of intestine in 25 dogs; 21 died with peritonitis—84.0 per cent. Among 19 dogs given similar injections and treated with the sulfanilamide group of drugs only 9 died with peritonitis—47.4 per cent; among 21 dogs given sulfathiazole 17 died with peritonitis—66.6 per cent; among 24 dogs given sulfadiazine 14 died with peritonitis—58.3 per cent. Penicillin was not tried. Bigger [340] has apparently confirmed the observation of Ungar on the synergistic action of penicillin and sulfonamide compounds.

Pseudomyxoma Peritonei.—In 3,087 cases in which appendectomy was performed, mucocele was encountered five times, an incidence of 0.13 per cent. A ruptured mucocele with pseudomyxoma peritonei is described.[341]

Carcinoma.—Chomet [342] reports 3 cases of carcinoma of the appendix; in 2 a clinical diagnosis of appendicitis was made; in the third the tumor was removed incidentally at the time of a hysterectomy.

LARGE INTESTINE (CECUM, COLON, RECTUM)

Epidemic Diarrhea of the Newborn.—Campbell [343] analyzes an outbreak of epidemic diarrhea occurring in 50 newborn infants in Australia. The explosive rapidity with which the disease spreads is spectacular. The stools are fluid, resembling yellow water, with no solid constituents. The value of parenteral fluids is great; sulfaguanidine is considered to have a definite beneficial effect. The mortality is higher in premature than in full term infants. The etiologic agent is unknown, and the mode of spread is uncertain, although certain signs suggest that it

338. Palmer, W. L., and Ricketts, W. E.: Chronic Ulcerative Colitis with Generalized Peritonitis and Recovery, Arch. Surg. **51**:102-105 (Sept.) 1945.

339. Daniel, R. A., Jr., and Holbrook, T. J.: The Prevention of Staphylococcus Infections of the Peritoneum, Surgery **17**:39-46, 1945.

340. Bigger, J. W.: Synergic Action of Penicillin and Sulphonamides, Lancet **2**:142-145, 1944.

341. Timoney, F. X.: Ruptured Mucocele of the Appendix with Pseudomyxoma Peritonei, Am. J. Surg. **64**:417-419, 1944.

342. Chomet, B.: Carcinoma of Appendix, Am. J. Clin. Path. **14**:447-451, 1944.

343. Campbell, K. I.: Report on an Outbreak of Epidemic Diarrhea of the Newborn, M. J. Australia **1**:79-84, 1945.

may be air borne. Menchaca [344] on the basis of 20 cases concludes that sulfadiazine is efficacious in the treatment of diarrhea of infants.

Virus Diarrhea.—Reimann, Hodges and Price [345] describe a mild epidemic disease characterized by anorexia, malaise, diarrhea, nausea and vomiting occurring in October and November of both 1943 and 1944 in Philadelphia. The infection is thought to have been an air-borne one; the etiologic agent is unknown.

Staphylococcic Food Poisoning.—An outbreak of food poisoning due to infected ham is described. The possible source of the infection was a food handler who carried an enterotoxin-producing strain of Staphylococcus aureus in his nasopharynx.[346]

Salmonella Infections.—Stewart and Slack [347] report a mild outbreak of food poisoning due to Salmonella Oranienburg present in veal salid. Two hundred men were affected. The source was not determined. Greifinger and Silberstein [348] report 115 cases of acute gastroenteritis in military personnel. S. Oranienburg was isolated in 86.9 per cent, S. typhimurium in 23.5 per cent and S. anatus in 38.2 per cent. S. Oranienburg persisted in the feces for thirteen weeks, S. anatus for eleven weeks and S. typhimurium for five weeks. Succinylsulfathiazole in adequate dosage had a bacteriostatic effect on the first two, aiding in the termination of the carrier state.

Lieberman [349] attributes an attack of acute bacillary dysentery to Bacillus alkalescens (Shigella alkalescens). In the feces of 3 patients with continued fever of the enteric type Raeburn found an organism resembling and probably identical with Bacillus faecalis alcaligenes (Alkaligenes faecalis).[350] Silverman and Leslie [351] report 4 instances of intestinal infection simulating chronic bacillary dysentery but pro-

344. Menchaca, F. J.: Sulfadiazine in the Treatment of Diarrhea in Children, Am. J. Dis. Child. **68**:5-6 (July) 1944.

345. Reimann, H. A.; Hodges, J. H., and Price, A. H.: Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, J. A. M. A. **127**:1-6 (Jan. 6) 1945.

346. Rutherford, P. S., and Crowson, C. N.: The Bacteriology of an Epidemic of Staphylococcal Food Poisoning, Canad. M. A. J. **52**:19-20, 1945.

347. Stewart, J. K., and Slack, J. M.: Salmonella Food Poisoning, Bull. U. S. Army M. Dept., 1945, no 88, pp. 120-122.

348. Greifinger, W., and Silberstein, J. K.: Salmonella Food Infection in Military Personnel: An Outbreak Caused by S. Oranienburg, S. Typhi Murium and S. Anatum, J. Lab. & Clin. Med. **29**:1042-1053, 1944.

349. Lieberman, W.: Acute Bacillary Dysentery Due to Bacillus Alkalescens, Rev. Gastroenterol. **12**:123-125, 1945.

350. Raeburn, C.: An Enteric-like Infection Due to B. Faecalis Alkaligenes, J. Roy. Army M. Corp. **63**:151-152, 1944.

351. Silverman, D. N., and Leslie, A.: The Simulation of Chronic Bacterial Dysentery by Paratyphoid B. Infection, Gastroenterology **4**:53-60, 1945.

duced by Bacillus parathyphosus B (Salmonella paratyphi B). Wang [352] tested 30 samples of Chinese soybean sauce made with water from shallow wells in China and found that 35 per cent were contaminated with Escherichia coli, Eberthella typhosa, Shigella dysenteriae or other Salmonelleae.

Barnes [353] presents evidence that certain members of the paracolon, Proteus and Pseudomonas groups of micro-organisms may be able, under certain conditions, to initiate outbreaks of gastroenteritis, diarrhea or dysentery-like disturbances. He further suggests that the terms "paratyphoid bacilli" and "paratyphoid fever" should be discarded in favor of "salmonellas" and "salmonelloses," respectively, since the former names are "restricted," ambiguous and obsolete." A list of the types of salmonellas known at the present time is included.[354] Michael and Harris [355] suggest that normal nonpathogenic organisms of the paracolon bacilli group may cause acute gastroenteritis under conditions of poor sanitation.

A diet of whole wheat and whole dried milk was shown to promote a higher survival rate among W-Swiss mice subjected to Salmonella enteritidis infections than that given by a synthetic diet. The unknown nutritional factors present in whole wheat are absent or negligible in dried whole milk.[356]

Bacterial Dysentery.—(*a*) Incidence: In the Navy the curve of hospitalization rates for diarrheal disease decreased gradually from 84.38 in 1882 to 10.01 in 1913. Definite progress since 1913 can be demonstrated only in the typhoid-paratyphoid, or salmonella, infections. Since 1922 the admission rates for chronic diarrheal diseases, cause unspecified, have definitely increased. Similarly, since 1914 the admission rates for diarrheal diseases caused by food-borne organisms, toxins or poisons have definitely increased. Further progress is thought to depend on the development of specific immunization against organisms causing bacillary dysentery and all food-borne organisms and toxins.[357] Of impor-

352. Wang, C. I.: Chinese Soy Bean Sauce as a Transmitting Agent of Bacterial Gastrointestinal Infections, Am. J. Trop. Med. **25**:47-50, 1945.

353. Barnes, L. A.: Pathogenic Enteric Bacilli: Paracolon, Proteus and Pseudomonas Groups, U. S. Nav. M. Bull. **43**:707-716, 1944.

354. Barnes, L. A.: Pathogenic Enteric Bacilli: The Salmonella Group, U. S. Nav. M. Bull. **43**:939-949, 1944.

355. Michael, M., Jr., and Harris, V. T.: Paracolon Bacilli: A Study of Fifty-Three Isolated Strains, with a Note on Pathogenicity, War Med. **7**:108-115 (Feb.) 1945.

356. Schneider, H. A., and Webster, L. T.: Nutrition of the Host and Natural Resistance to Infection, J. Exper. Med. **81**:359-384, 1945.

357. Smiley, D. F., and Raskin, H. A.: Diarrheal Diseases in the Navy: The Navy's Experience, 1882-1942, U. S. Nav. M. Bull. **44**:267-283, 1945.

tance in this respect is the work of Cooper and his associates.[358] Blood obtained from children immunized with killed suspensions of dysentery bacilli showed an increase in passive mouse-protective power ranging from thirteen fold to six hundred and forty-five fold. This protective power decreased gradually but was present in an appreciable degree after twenty-four weeks. Homologous was always greater than heterologous immunity. The results suggest that active immunization with combined antigens may offer protection for a few weeks or months. Volunteers immunized with the purified specific antigen of type V Shigella paradysenteriae (Flexner) by Perlman and co-workers [359] had a high titer of bacterial agglutinins and mouse-protective antibodies. The titer fell moderately in six months and then rose fairly well in response to a small recall dose of the antigen.

Hurevitz [360] concludes that, "of all noncombat casualties, bacillary dysentery is proving one of the most significant causes for disability among troops in this war, as it has in all other wars." Sanitary discipline is the most important factor in its prevention. Of 1,120 patients with diarrhea admitted to an overseas station hospital between May 1 and November 1, 567 had stool cultures positive for bacillary dysentery, 409 (69.8 per cent) harboring Shigella paradysenteriae. Pot [361] found that in Curaçao bacillary dysentery is one of the most frequent infectious diseases, 429 cultures of various strains of Shigella paradysenteriae having been obtained in 2,753 stool examinations.

(*b*) Transmission: In an evaluation of the various factors in the cases of dysentery seen in the South Pacific, Calarco [362] considers the common fly as "the main vector in the transmission of bacillary dysentery" and contaminated food as the chief source of amebic dysentery, although the importance of all sanitary measures is emphasized. Sulfonamide compounds are recommended for the therapy of severe bacillary dysentery, emetin hydrochloride and carbarsone for that of amebic dysentery. The difficulties presented by combined infections may be rather great.

358. Cooper, M. L.; Tepper, J., and Keller, H. M.: Active Immunization of Children with Shigella Paradysenteriae and Shigella Sonnei, Proc. Central Soc. Clin. Research **17**:68, 1944.

359. Perlman, E.; Binkley, F., and Goebel, W. F.: Studies on the Flexner Group of Dysentery Bacilli: III. Antibody Response in Man Following the Administration of the Specific Antigen of Type V Shigella Paradysenteriae (Flexner), J. Exper. Med. **81**:349-358, 1945.

360. Hurevitz, H. M.: Bacillary Dysentery, War Med. **6**:247-250 (Oct.) 1944.

361. Pot, A. W.: Bacillary Dysentery in Curaçao, Netherlands West Indies, Am. J. Digest. Dis. **12**:70-73, 1945.

362. Calarco, J. J.: The Dysenteries, M. Clin. North America **28**:1497-1508, 1944.

In North Africa dysentery bacilli were found by Stewart [363] to be viable in feces eleven days after passage under natural conditions of drying. In rain water Flexner organisms were viable for thirty-eight days. Carriers in the native population of North Africa were found to constitute an important source of infection, and flies, an important means of transmission. It was shown that flies could transmit bacilli from dried feces to the culture plates for as long as eleven to twelve days after passage of the feces.

Fairbrother [364] reports that Shigella dysenteriae was isolated from the feces on 245 occasions in a group of 2,500 apparently healthy Italian prisoners of war, an incidence of carriers of 10 per cent. All carriers were given a routine course of sulfaguanidine, 6 Gm. three times on the first day and 3 Gm. three times daily for the next five days, making a total dose of 63 Gm. in six days. The treatment appeared to be successful in 227 cases; in the 16 failures the types found were Flexner (12 cases), Shiga (2) and Sonne (2). In the majority of these cases the response to the second course of sulfaguanidine was satisfactory. Jacoby and associates [365] emphasize the importance of control of flies, careful bacteriologic examination of food handlers, strict care in the preparation of all foods containing meat, milk, eggs and mayonnaise, and chlorination of water. A combination of sulfathiazole and sulfaguanidine is considered most effective in treatment; it lowered the period of hospitalization from 7.2 to 5.0 days, and cleared 96 per cent of the infections within six days, for the 47 patients so treated.

Sandweiss [366] has analyzed the hazard presented by carriers of dysentery shigellas who serve as food handlers. He pleads for a comprehensive national program of prevention of dysentery, for more rigid rules in the examination of food handlers and for more frequent follow-ups of all persons found to be carriers.

(*c*) Treatment: In War Department Technical Bulletin no. 119, in the section dealing with the treatment of bacillary dysentery emphasis is laid on hydration and chemotherapy (sulfadiazine being suggested as the drug of choice, and sulfathiazole, succinylsulfathiazole and sulfaguanidine as less satisfactory substitutes). Penicillin is not effective. Serum therapy is apparently of little value. Rest in bed and isolation

363. Stewart, W.: On the Viability and Transmission of Dysentery Bacilli by Flies in North Africa, J. Roy. Army M. Corp. **63**:42-46, 1944.

364. Fairbrother, R. W.: The Control of Bacillary Dysentery, Brit. M. J. **2**:489-492, 1944.

365. Jacoby, A. H.; Loudon, J. R.; Wyne, P. S., and Failmezger, T. R.: The Diarrhea Problem in a New Guinea Base, Bull. U. S. Army M. Dept., 1945, no. 86, pp. 70-78.

366. Sandweiss, D. J.: Diarrhea and Bacillary Dysentery in Detroit: A Study of the Effect of Sulfathalidine on Bacillary Dysentery Carriers, Clinics **3**:553-576, 1944.

are important. Purgation and enemas are contraindicated. Strict attention to prophylactic measures, such as isolation, sewage disposal, disinfection of bedding and dishes, maintenance of a proper food and water supply, instruction of food handlers, fly control, screening and the use of DDT spray are emphasized. The practical value of immunization has not been demonstrated.[367]

Felsen [368] summarizes the present knowledge of the action of sulfonamide compounds and advises that an initial dose of 0.25 Gm. per kilogram of body weight be given during the first twenty-four hours in divided doses, one every four hours, and that thereafter half of this dose be given daily until the symptoms recede and for a minimum of several days. Beneficial effects in varying degrees are obtained with both the poorly and the readily absorbed sulfonamide drugs. There is some evidence that a combination of these two types may be more desirable for general use than either type alone. Scott [369] finds that for patients with mild bacillary dysentery the mean length of stay in the hospital is decreased from 12.7 to 11.6 days by the use of sulfaguanidine and the discontinuation of saline purgation. It is not clear how much of the slight decrease is to be attributed to the drug and how much to the discontinuance of purgation. Ferriman and Mackenzie [370] compare the effects of different sulfonamide compounds in 56 cases and find that the average time of recovery is three to six days (18 cases) for sufanilamide, three to four days (18 cases) with sulfaguanidine and two to seven days (20 cases) with sulfathiazole. In vitro studies of the action of various sulfonamide compounds on Shigella dysenteriae afford evidence that sulfathiazole and sulfadiazine give the best results while sulfaguanidine is relatively ineffective.[371]

On the other hand, Fortune and Ferris [372] on the basis of an experience with 2,810 cases of bacillary dysentery in New Guinea consider sulfaguanidine administered in a dose of at least 90 Gm. over a period of seven days the treatment of choice when the infection is in an early stage.

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367. Bacillary Dysentery, United States War Department, Technical Bulletin (TB Med 119), War Med. **7**:36-39 (Jan.) 1945.

368. Felsen, J.: VII. Effects of the Sulfonamides in Bacillary Dysentery, Gastroenterology **4**:14-16, 1945.

369. Scott, R. B.: On the Effect of Sulphaguanidine in Acute Bacillary Dysentery, J. Roy. Army M. Corp. **64**:159-162, 1945.

370. Ferriman, D. G., and Mackenzie, G. K.: Comparison of Sulphonamides in Bacillary Dysentery, Lancet **2**:687-688, 1944.

371. Beemer, A. M. A., and Fairbrother, R. W.: The In-Vitro Activity of Various Sulphonamides on Bact. Dysenteriae, J. Path. & Bact. **56**:567-569, 1944.

372. Fortune, C., and Ferris, A. A.: Diarrhoeal Diseases in New Guinea, M. J. Australia **1**:337-344, 1945.

(*d*) Basteriophage: Morton and Engley [373] review the status of bacteriophage in bacillary dysentery and conclude that while the evidence regarding its therapeutic use is inconclusive, the results in prophylaxis are encouraging.

(*e*) Streptomycin: Reimann and his co-workers [374] report that oral administration of streptomycin suppresses the growth of Escherichia coli and Eberthella typhosa (Salmonella typhi) in the feces.

(*f*) Typhoid with Perforation: Scott and Ortner [375] describe successive multiple intestinal perforations from typhoid occurring in an 11 year old boy. Administration of sulfathiazole and succinylsulfathiazole in conjunction with the surgical repair of the perforation resulted in recovery. A similar case is reported by Dubrow.[376]

Parasitic Dysentery.—The excellent manual of tropical medicine prepared by Mackie, Hunter and Worth [377] under the auspices of the National Research Council is well worth the study of all interested in this field. Turner,[378] who has had extensive experience with tropical and parasitic medicine, gives an excellent review of the various types of dysentery.

Bailey [379] calls attention to the prevalence of intestinal parasites throughout the Southeastern United States. The soil and the climate of Kentucky are particularly conducive to unusually heavy infection. Elimination of infection may be accomplished through proper drainage of the soil and proper care of the latrines of the community. Ascaris lumbricoides is the most common infectious agent in children; Trichuris trichiura and Necator americanus, the most prevalent in adults. Treatment is not highly successful, because complete elimination of the infection is difficult. Nevertheless, the infection may be reduced sufficiently to free the patient from disease. Of 1,452 patients examined in an

373. Morton, H. E., and Engley, F. B.: Dysentery Bacteriophage: Review of the Literature on Its Prophylactic and Therapeutic Uses in Man and in Experimental Infections in Animals, J. A. M. A. **127**:584-591 (March 10) 1945.

374. Reimann, H. A.; Elias, W. F., and Price, A. H.: Streptomycin for Typhoid: A Pharmacologic Study, J. A. M. A. **128**:175-180 (May 19) 1945.

375. Scott, E. P., and Ortner, A. B.: Typhoid: Successive Intestinal Peforations with Recovery, Am. J. Dis. Child. **68**:119-121 (Aug.) 1944.

376. Dubrow, A. A.: Perforation of the Intestine Due to Typhoid, J. A. M. A. **126**:495-496 (Oct. 21) 1944.

377. Mackie, T. T.; Hunter, G. W., and Worth, C. B.: A Manual of Tropical Medicine, National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1945.

378. Turner, E. L.: The Dysenteries, Ohio State M. J. **40**:1133-1139, 1944; Amebiasis; Other Intestinal Protozoal Infections; Helminthous Dysentery, Kentucky M. J. **42**:135-143, 1944; Bacillary Dysentery, ibid. **42**:95-101, 1944.

379. Bailey, W. C.: A Study of the Incidence and Treatment of Intestinal Parasites in Southeastern Kentucky, South. M. J. **37**:407-409, 1944.

institution for patients with tuberculosis, 64 (4.4 per cent) harbored parasites: Strongyloides, N. americanus, Endamoeba coli, Ascaris lumbricoides, T. trichiura and Hymenolepis nana.[380]

Of 161 children infected with multiple parasites, 119 (74 per cent) were brought to the hospital for other conditions, although the diseases of 26 per cent later were shown to be due to parasitism alone. Vomiting, vomiting of worms, fever, diarrhea, anorexia, abdominal pain and passage of worms are the most frequent manifestations. Eosinophilia occurred in less than 20 per cent of the patients. Hexylresorcinol was the most effective vermifuge for ascariasis and tetrachloroethylene the most effective for ancylostomiasis. Sanitary disposal of feces is vital for the prevention of infection.[381]

Markell [382] analyzes the results of 2,388 examinations of stools made by means of the direct centrifugal flotation method of Faust and 1,371 examinations of wet smears in New Zealand. Intestinal parasites were found in 28 per cent. The zinc sulfate technic combined with iron-hematoxylin staining of smears demonstrated an average of 36 per cent of the E. histolytica infections with a single examination, 59 per cent with two examinations and up to 93 per cent with six examinations. With three examinations 85 per cent of the nonpathogenic amebic infections were demonstrated. Only 20 per cent of the patients entered the hospital with gastrointestinal complaints. Of the total, 8.46 per cent had hookworm infection; 8.09 per cent, E. histolytica infection, and 22.15 per cent, E. nana—an incidence about twice the average found within the continental United States. A survey of intestinal parasites among 125 Melanesians disclosed a high incidence of hookworm infection together with a moderately high incidence of infections with A. lumbricoides and T. trichiura.[383]

Wirts and Tallant [384] in the Middle East found that approximately 12 per cent of patients harbored one or more forms of intestinal parasite and 23 per cent a bacillary pathogen, predominantly Shigella paradysenteriae Flexner.

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380. Habeeb, W. J.: Human Intestinal Parasites in a West Virginia Tuberculosis Institution, South. M. J. **37**:701-703, 1944.

381. Einhorn, N. H.; Miller, J. F., and Whittier, L.: Intestinal Polyparasitism: Clinical Survey of One Hundred and Sixty-One Cases of Infection with Multiple Intestinal Parasites in Children, Am. J. Dis. Child. **69**:350-358 (June) 1945.

382. Markell, E. K.: Intestinal Parasitic Infections in a Naval Hospital in New Zealand, U. S. Nav. M. Bull. **44**:65-68, 1945.

383. Russell, H. K., and Scott, J. O.: Intestinal Parasites Among Melanesians, U. S. Nav. M. Bull. **44**:727-728, 1945.

384. Wirts, C. W., Jr., and Tallant, E. J.: Dysentery in American Troops in the Middle East, Am. J. Digest. Dis. **11**:252-255, 1944.

(*a*) Amebiasis: Craig,[385] the outstanding authority in this field, has published a new book on the causation, the diagnosis and the treatment of amebiasis. While it cannot be reviewed here, it can, nevertheless, be recommended most highly.

In a splendid experimental study Chang [386] has shown that a strain of E. histolytica may lose its infectivity and some of its pathogenicity for kittens after a long period of cultivation without encystment, that the infectivity of the noninfective cultural strains can be restored by encystment, that the presence of a virulent bacterial flora may not increase the infectivity for kittens of noninfective cultural strains of E. histolytica and that in studying the virulence of cultural strains of E. histolytica, distinction should be made between infectivity and pathogenicity.

Of 112 patients admitted to a military center for patients with tropical diseases in England, who were suffering from dysentery or its effects, 33 were found to have amebiasis. Of these, only 7 had had recent diarrhea and in 14 diarrhea had never been prominent. Emetine bismuth iodide given orally and emetine bismuth iodide with chiniofon administered rectally gave the most permanent cures.[387]

Browne, McHardy and Spellberg [388] studied 3,984 ambulatory patients with amebiasis. In office patients the incidence was 14.1 per cent, in contrast with 5.2 per cent in hospital patients. Roentgen examination (barium sulfate enema) disclosed changes consistent with amebic colitis in 35.5 per cent. In 42.2 per cent of the patients with active dysentery ulcers were seen on proctoscopic examination. Taubenhaus [389] emphasizes the importance of amebiasis as a cause of recurrent abdominal pain and mild diarrhea.

In the dysentery ward of a forward British field hospital in an undisclosed location 2,114 patients with diarrhea were admitted, 370 of whom were found to have bacillary dysentery (7, or 1.8 per cent, died) and 701 amebic dysentery (10, or 1.4 per cent, died). Four of the 10 had perforation and 1 gangrene of the descending colon. There were 68 patients with amebic hepatitis and amebic abscess. Almost half of the

385. Craig, C. F.: The Etiology, Diagnosis and Treatment of Amebiasis, Baltimore, Williams & Wilkins Company, 1944.

386. Chang, S. L.: Studies on Entamoeba Histolytica: V. On the Decrease in Infectivity and Pathogenicity for Kittens of E. Histolytica During Prolonged in Vitro Cultivation and Restoration of These Characters Following Encystment and Direct Animal Passage, J. Infect. Dis. **76**:126-134, 1945.

387. Bomford, R. R.: Chronic Amoebiasis in Soldiers, J. Roy. Army M. Corp. **83**:279-283, 1944.

388. Browne, D. C.; McHardy, G., and Spellberg, M. A.: Statistical Evaluation of Amebiasis, Gastroenterology **4**:154-163, 1945.

389. Taubenhaus, L. J.: Amebiasis as Cause of Recurrent Abdominal Pain: Report of Cases, U. S. Nav. M. Bull. **43**:527-531, 1944.

patients suffered from a nonspecific diarrhea. [This observation is of great interest to the reviewers because of the possibility that these patients may have had chronic nonspecific colitis as a sequel, a nonspecific infectious sequel, of a specific infection. The suggestion is, of course, not new, but to us it has never been satisfactorily proved or disproved.[390] It comes to mind again in connection with Bloom's [391] observations on 250 British prisoners of war from prison camps in North Africa. On arrival they were emaciated and apathetic, suffering severely from dysentery, often with incontinence. Various symptoms and signs of vitamin deficiency were noted. E. histolytica was demonstrated in the feces, but the patients did not improve clinically under treatment with emetine. The continued dysentery is attributed to mixed infection of the intestine occurring in men weakened by starvation and with little resistance to organisms ordinarily nonpathogenic. The relatively rapid development of vitamin deficiencies and their persistence for months in spite of an adequate intake of vitamins are attributed to malnutrition and poor absorption from an atrophied and ulcerated bowel. In the treatment of these chronic infections diet proved the most important factor. Meat was much more readily assimilated than milk even when the disease was extensive. Milk in large quantities may be definitely harmful. The condition of many of the men apparently had been made worse by indiscriminate dosing with "salts." This is considered a dangerous practice. Sulfaguanidine appeared to be remarkably beneficial.]

Halpert and Ashley [392] add 1 case to the 61 cases of amebic abscess of the brain recorded in the literature.

Emetine has no rival in the treatment of the acute symptoms of intestinal amebiasis and hepatitis even in the presuppurative phase. On the other hand, in 126 patients with chronic amebiasis treated by D'Antoni with diodoquin 92 per cent effectiveness was observed with a single course and 99 per cent effectiveness with two or more courses.[393]

(*b*) Giardiasis: Welch,[394] studying 29 cases of giardiasis, found in 73 per cent roentgenographic evidence of changes in the mucosal pattern and in the motor functions of the duodenum, the duodenal cap

390. Miller, F. G.: The Treatment of Dysentery in a Forward Hospital, J. Roy. Army M. Corp. **64**:171-174, 1945.

391. Bloom, H.: Dysentery in British Prisoners of War, Lancet **2**:558-560, 1944.

392. Halpert, B., and Ashley, J. D., Jr.: Amebic Colitis Complicated with Abscess of the Brain, Arch. Path. **38**:112-114 (Aug.) 1944.

393. Arosemena, J.: The Treatment of Amebiasis, New Orleans M. & S. J. **97**:392-400, 1945.

394. Welch, P. B.: Giardiasis with Unusual Findings, Gastroenterology **3**:98-102, 1944.

and the pyloric and prepyloric area. Eosinophilia was present in 75 per cent. Weingarten and Rosenfeld [395] report an interesting case in which a 30 year old pregnant woman with vomiting from the fourth to the eighth month of pregnancy was shown by means of biliary drainage to have giardiasis. Under treatment with quinacrine hydrochloride the symptoms disappeared entirely.

(*c*) Ancylostomiasis and Strongyloidiasis: A study of 71 children with ancylostomiasis revealed marked absence of symptoms referable to hookworm infection, although 1 patient had severe anemia. The degree of infection, i. e., the number of worms present, was not determined. Apparently all the patients had light "worm burdens"; this may account for the low incidence of symptoms. In 4 children with strongyloidiasis, on the other hand, diarrhea and vomiting were present.[396]

(*d*) Pinworms: Of 1,871 persons examined for pinworms in a state hospital, 1,100 were infected, the incidence being 72 per cent among the patients with chronic mental diseases and 1 per cent among inebriates. None of the employees was infected. One course of gentian violet medicinal (methylrosaniline chloride U. S. P.) provided effective treatment in 91 per cent of the patients. Of 208 reexamined in ten months, 77 (37 per cent) were infected.[397]

Miller and Einhorn [398] in a study of 200 children with pinworms emphasize the diagnostic assistance of the cellophane tip. Treatment was not entirely satisfactory, although gentian violet medicinal appeared to be the best disinfectant tried. However, it can be used only with older children, who, after all, do not constitute a majority of the patients with symptoms. Occasionally, even older children cannot retain the drug because of vomiting. Quassia enemas proved valuable, especially for infants and younger children. This method was troublesome to the mothers, and while it relieved symptoms, it did not always cure the infection. Tetrachloroethylene was of no value.

(*e*) Schistosomiasis Mansoni: In Puerto Rico 10 per cent of healthy male inductees for selective service were shown to have ova of Schis-

395. Weingarten, M., and Rosenfeld, S.: Persistent Vomiting Due to Giardiasis, Am. J. Digest. Dis. **12**:54-55, 1945.

396. Miller, J. F.; Einhorn, N. E., and Whittier, L.: Ancylostomiasis and Strongyloidiasis: A Clinical Survey of Seventy-One Cases of Ancylostomiasis and Eleven Cases of Strongyloidiasis in Children, Am. J. Dis. Child. **69**:359-365 (June) 1945.

397. Petersen, M. C., and Fahey, J.: Oxyuriasis: Simplified Method of Diagnosis with Glass Slide; Incidence in a Minnesota State Hospital; Result of Treatment with Gentian Violet, J. Lab. & Clin. Med. **30**:259-261, 1945.

398. Miller, J. F., and Einhorn, N. H.: Oxyuriasis: A Clinical Survey of Two Hundred Consecutive Cases of Infection with Enterobius Vermicularis in Children, Am. J. Dis. Child. **68**:376-381 (Dec.) 1944.

tosoma mansoni on routine examination of stools. Proctoscopic examination of 155 infected men revealed ulceration of the rectal mucosa in 60.7 per cent. The mucosa was generally soft, velvety and pale pink, with single or multiple ulcers either pinpoint or linear in shape. The ulcerated area was sharply demarcated from the surrounding normal mucosa, with no zone of inflammation, no crater or ragged edges and no exudate. The ulcer was a noninflammatory break in the continuity, through which oozed a small amount of blood. It was located at the bifurcation of capillaries or was lying directly on them. This relationship of the ulcers to the blood vessels was so constant that a definite relationship could be established. When the ulcers were numerous, they outlined the pattern of the capillaries. The ulcers were below the rectosigmoid fold. Polyps were seen in only 2 instances. Infection with S. mansoni indicates schistosomiasis, for there are no healthy carriers.[399]

Bercovitz, Shwachman and Rodriguez-Molina [400] analyzed the blood picture in 147 Puerto Rican young men who had no clinical symptoms but in whom infection with S. mansoni as well as other intestinal parasites was found. Of 17 infected with S. mansoni alone, 5 had leukocytosis and 6 eosinophilia, the highest count of eosinophils being 14 per cent. In 3 no eosinophils were found. In spite of the various parasitic infections present, the blood picture showed a striking resemblance to that in 450 healthy Puerto Rican males free from intestinal and hematogenous parasites.

In 2 cases Di Giacomo and Mayer [401] noted improvement after treatment with fuadin. They emphasize the desirability of obtaining a stool, following the administration of a saline purge, from every person returning to this country.

Colonic Diseases.—(*a*) Functional Disorders: Jordan [402] in discussing the problems which the gastroenterologist will face after the war concludes that the chief ones will probably be the functional digestive disorders and peptic ulcer, both of which may have urgent social and economic implications. She emphasizes the common failure to recognize that disordered digestive function readily becomes habitual. Rest is

399. Bercovitz, Z. T.; Rodriguez-Molina, R.; Hargrave, D. W.; Dickie, J. D., and Green, C. E.: Studies on Human Schistosoma Mansoni Infections: I. Proctoscopic Picture in Asymptomatic Schistosomiasis Mansoni Infections, J. A. M. A. **125**:961-963 (Aug. 5) 1944.

400. Bercovitz, Z. T.; Shwachman, H., and Rodriguez-Molina, R.: The Blood Picture in Asymptomatic Schistosoma Mansoni and Other Intestinal Parasitic Infections, Am. J. Trop. Med. **25**:41-45, 1945.

401. Di Giacomo, M. P., and Mayer, R. A.: Schistosomiasis Mansoni, J. A. M. A. **125**:904 (July 29) 1944.

402. Jordan, S. M.: Presidential Address: Post-War Rehabilitation of the Digestive Tract, Gastroenterology **3**:73-78, 1944.

the best restorative measure. Peters and Bargen [403] give an excellent detailed discussion of the syndrome of the irritable bowel.

Kiefer [404] in analyzing the differential diagnosis of disorders of the small and the large bowel emphasizes the fact that predefecation pain which is relieved by passage of stool or of gas usually is colonic in origin. Pain of the right upper quadrant of the abdomen is common in disorders of the colon; chronic persistent pain of the right lower quadrant of long standing suggests irritation of the cecum rather than appendical inflammation; pain of the lower left quadrant is perhaps more typical of spasticity of the colon, and the classic discomfort of large bowel origin usually is felt across the lower part of the abdomen or even in the back. On the other hand, pain arising from the small bowel has a tendency to be most intense in the upper part of the abdomen or in the periumbilical region.

A physiologic study made by Peterson and Youmans [405] on the intestinointestinal inhibitory reflex in unanesthetized dogs is of considerable clinical significance. The minimal pressure required to produce a reflex inhibition of intestinal motility falls as the length of the distended jejunum is increased. The intestinal segment then becomes sensitized to redistention, and the same inhibition can be produced with less pressure. The mechanism of action seems to be that of peripheral sensitization occurring at the site of distention. This may represent in part the mechanism or the physiologic basis of irritability of the colon. Of similar physiologic and clinical interest and importance is the observation by Barker [406] of acute colitis following a soapsuds enema. The colitis was characterized by pain, the passage of serosanguineous fluid and roentgen evidence of extreme irritability and spasm. Jones,[407] on the other hand, emphasizes the role of emotional tension and presents some interesting cases together with instructive comment. Similarly Alvarez [408] describes patients without organic disease whose symptoms are aggravated by emotional stress. Reassurance, a low residue diet and sedatives are recommended.

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403. Peters, G. A., and Bargen, J. A.: The Irritable Bowel Syndrome, Gastroenterology **3**:399-402, 1944.

404. Kiefer, E.: Diagnosis of Disorders of the Small and Large Intestine, New York State J. Med. **44**:2342-2349, 1944.

405. Peterson, C. G., and Youmans, W. B.: The Intestino-Intestinal Inhibitory Reflex: Threshold Variations, Sensitization and Summation, Am. J. Physiol. **143**: 407-412, 1945,

406. Barker, C. S.: Acute Colitis Resulting from Soapsuds Enema, Canad. M. A. J. **52**:285, 1945.

407. Jones, C. M.: Functional Gastro-Intestinal Disturbances, M. Clin. North America **28**:1154-1163, 1944.

408. Alvarez, W. C.: Distress after Defecation, Clinics **3**:577-581, 1944.

(*b*) Constipation: McGuigan and associates [409] think that habitual constipation is a common disorder which frequently requires laxative drugs for its treatment. The U. S. P. dose of phenolphthalein (0.06 Gm.) or of aromatic fluid extract of cascara sagrada (2 cc.) is ineffective. Optimal doses are 0.20 Gm. of phenolphthalein and 4 cc. of aromatic fluidextract of cascara sagrada. [The reviewers are of the opinion that the need for this form of treatment is not as common as it is alleged to be. The great majority of persons complaining of constipation are in reality victims of the syndrome of the irritable bowel. However, for some patients the continued use of phenolphthalein and cascara is permissible.]

(*c*) Megacolon: Grimson and his associates [410] in discussing their experience in 24 cases of Hirschsprung's disease divide the patients into three groups:

Group 1. These patients have uniform involvement of the entire colon terminating in a dilated or easily dilatable rectum. Eight of twelve such patients are now living and are evacuating their colons readily, at an average age of 10 years. One died three years after undergoing sympathectomy, at the age of 24. Of the remaining 3, 1 is having moderately severe trouble at the age of 6, 1 required surgical reduction of a volvulus of the sigmoid at the age of 20 and 1 underwent reduction of a volvulus of the sigmoid at the age of 59, with a recurrence three months later and resection. It appears that protracted medical management of the patients of this group is indicated as long as adequate nutrition can be maintained and persistent abdominal distention avoided. Sympathectomy does not alter significantly the gross pathologic condition, and by interrupting visceral sensory pathways it may permit negligence on the part of the patient with the development of serious impactions. Segmental resection of the colon, as reported in the literature, has been followed frequently by recurrence of impactions proximal to the anastomosis. It would therefore seem that resection of the colon, if indicated for a patient with this condition, should start at the cecum and continue distally through the proximal divisions of the colon to the sigmoid, in order that the liquid contents of the ileum may empty into the remaining, and preferably rather short, segment of the involved bowel.

Group 2. These patients have uniform dilatation of the proximal segments of the colon terminating in a normal segment of bowel, usually

409. McGuigan, H. A.; Steigmann, F., and Dyniewicz, J. M.: Evaluation of the Laxative Effect of Some Commonly Used Laxative Substances, with Particular Reference to Dosage, Am. J. Digest. Dis. **11**:284-289, 1944.

410. Grimson, K. S.; Vandegrift, H. N., and Dratz, H. M.: Management and Prognosis of Megacolon (Hirschsprung's Disease), Am. J. Dis. Child. **68**:102-115 (Aug.) 1944.

in the sigmoid, and a normal rectum. Four of 7 such patients received conventional management and died, 2 at the age of 15 months, 1 at 9 years and 1 at 17 years. One underwent sympathectomy. The remaining 3, with equally severe symptoms and enormous colons, treated unsuccessfully by sympathectomy, underwent, at the ages of 2, 11 and 21, resection of the megacolon with anastomosis between the terminal portion of the ileum and the remaining stump. These 3 are living and well.

Group 3. The patients of this group have enormous enlargement of the sigmoid or of the sigmoid and descending colon, with or without involvement of the proximal portions of the colon and of the rectum. Of 5 such patients, at an average age of 16, 2 were free from symptoms and 3 had moderately severe symptoms. Three of these patients had definitely enlarged rectums and 1 a normal rectum; in 1, during the course of observation, the rectum, which had been normal, became enlarged, with relief of symptoms. Three of the patients independently, by trial and error, determined that laxatives taken once or twice a week produced more effective elimination than laxatives taken daily. The authors conclude that protracted medical management is justified in this group and that in patients with normal segments of the lower sigmoid and rectum these structures may become progressively dilated so that the massive evacuation of impacted material may be accomplished.

Penick [411] in the study of 11 cases of congenital megacolon treated by left lumbar sympathectomy reported 7 with highly successful results, 3 with great improvement and 1 with complete failure of treatment. Martin and Ward [412] describe a 22 year old man with megacolon, attributed to a stricture of the sigmoid; the stricture was resected successfully.

(*d*) Cecitis: Meyer and Disch [413] describe acute diffuse fatal phlegmonous cecitis.

Rosser [414] reports 2 cases of cecal ulcer clinically indistinguishable from carcinoma. The lesion is usually found on the mesial side of the cecum near the ileocecal valve; it is single, nonspecific and penetrating with a tendency to perforate and to cause extensive scarring. The causation is unknown.

The surgical treatment of benign lesions of the right (or ascending) side of the colon, particularly regional enteritis and granuloma of the cecum, is well presented in another paper.[415]

411. Penick, R. M., Jr.: Problems in the Surgical Treatment of Congenital Megacolon, J. A. M. A. **128**:423-426 (June 9) 1945.

412. Martin, J. D., Jr., and Ward, C. S.: Megacolon Associated with Volvulus of Transverse Colon, Am. J. Surg. **64**:412-416, 1944.

413. Meyer, L. M., and Disch, R.: Acute Phlegmonous Cecitis, Am. J. Surg. **68**:398-400, 1945.

414. Rosser, C.: Simple Penetrating Ulcer of the Cecum, Tr. South S. A (1943) **55**:89-95, 1944.

(Footnotes continued on next page)

(*e*) Intussusception and Volvulus of Cecum and Colon: Croce and Wiper [416] describe a cecocolonic intussusception without complete obstruction. No predisposing factor was discovered except the presence of a wide mesentery. Roentgenograms demonstrated the lesion after the use of oral and also rectal administration of barium sulfate.

Levitin and Weyrauch [417] discuss the differential roentgenologic diagnosis of volvulus and carcinoma of the sigmoid with acute obstruction. The pattern of the shadow of the colon is widest in the cecum in carcinoma, whereas in volvulus the involved loop of sigmoid becomes distended, rises out of the pelvis and lies in the midabdomen. Seven cases of carcinoma and 3 of volvulus are described.

(*f*) Perforation of Colon: The mortality from traumatic perforation of the colon was reduced from the 50 to 75 per cent range of World War I to 30 per cent in the recent conflict, although the morbidity rate was still high. In 21 cases studied by Colcock [418] retraction of the colostoma precipitated most of the complications. Traumatic perforations of the colon following intrarectal biopsy, enema and colonic irrigation, respectively, are reported.[419]

(*g*) Diverticulosis and Diverticulitis of Cecum and Colon: Noon and Schenk [420] describe 3 cases of solitary diverticulum of the cecum with diverticultis simulating appendicitis. Hendtlass [421] reports the perforation of such a diverticulum.

Martin and Adsit [422] in an excellent clinical study of diverticulosis, diverticulitis and carcinoma found that about 5 per cent of patients subjected to roentgen irradiation of the colon for any cause have diverticulosis. In 7,000 consecutive autopsies diverticulosis was present in 3.58 per cent of patients over 40 years. The incidence is 33 per cent higher in females than in males. Diverticulitis developed in 12 to 15

415. Rosser, C.: Benign Surgical Lesions of the Right Colon, J. A. M. A. **127**:568-571 (March 10) 1945.

416. Croce, E. J., and Wiper, T. B.: Cecocolic Intussusception in the Adult: Case Report, Am. J. Surg. **66**:389-392, 1944.

417. Levitin, J., and Weyrauch, H. B.: Acute Obstruction of the Colon: Differential Diagnosis Between Volvulus and Cancer of the Sigmoid Colon by Preliminary Roentgenogram, Am. J. Roentgenol. **53**:132-141, 1945.

418. Colcock, B. P.: Postoperative Problems Following Perforation of Colon, Army M. Bull. 1944, no. 80, pp. 106-108.

419. Kaufman, L. R.; Serpico, S., and Mosig, H. J.: Perforation of the Rectosigmoid, Surgery **17**:337-342, 1945.

420. Noon, Z. B., and Schenk, H. L.: Solitary Diverticulitis of the Cecum, Am. J. Surg. **68**:364-368, 1945.

421. Hendtlass, R. F.: Perforated Solitary Diverticulum of Caecum, Brit. M. J. **2**:309-310, 1944.

422. Martin, K. A., and Adsit, C. G.: Diverticulosis and Diverticulitis: A Clinical Study of the Complications, M. Clin. North America **29**:639-654, 1945.

per cent of patients with diverticulosis. At New York Hospital, in 177,718 admissions from 1933 to 1944, 201 cases of diverticulitis were encountered; 28 were of Meckel's type. Operation for some complication was performed in 51 cases, with 12 deaths (23.5 per cent). Carcinoma was observed in association with diverticulitis four times (7.8 per cent) and with diverticulosis thirteen times. Allen [423] states that 22 per cent of patients with diverticulitis come to operation because of acute perforation, obstruction of the sigmoid, fistula, localized abscess or inability to rule out carcinoma. A history of bleeding was obtained from 25 per cent. Lesions located in the sigmoid are the most favorable for surgical intervention. The trend is toward more radical surgical intervention with the first operation, i. e., resection of the involved segment at the time of exploration, rather than the two stage colostomy followed by resection.[424] Jones [425] likewise discusses the surgical treatment of inflammatory lesions of the colon.

Bonorino Udaondo [426] gives an excellent review of inflammation of the sigmoid part of the colon.

(*h*) Ulcerative Colitis: The increasing incidence of inflammatory disease of the colon is illustrated by the fact that 650 patients with colitis were seen at the Mayo Clinic in 1943; 520 with ulcerative colitis, 43 with intestinal tuberculosis; 82 with amebiasis and 5 with lymphopathia venereum.[427] Winkelstein [428] summarizes a discussion by stating that the disease is common, crippling and baffling in its nature, that it has a high mortality, that medical therapy has advanced chiefly in the use of transfusion and antitoxic B. coli serum and that surgical therapy is still on trial. All in all, ulcerative colitis remains definitely "colitis gravis."

Present knowledge of regional segmental ulcerative colitis derives largely from the excellent studies made by Bargen and his associates.[429] A recent report indicates that this condition was diagnosed in 68 patients —4 per cent of the total number with ulcerative colitis. With regard

423. Allen, A. W.: Abdominal Surgery, New England J. Med. **232**:165-173 1945.

424. Rosser, C.: Diverticulitis: Indications for Resection, South. M. J. **38**: 161-166, 1945.

425. Jones, T. E.: Inflammatory Lesions of the Colon, J. A. M. A. **126**: 1013-1015 (Dec. 16) 1944.

426. Bonorino Udaondo, C.: Las sigmoiditis infiltrantes y su tratamiento, Rev. de gastro-enterol. de México **9**:137-157, 1944.

427. Bargen, J. A.: Annual Report on Intestinal Diseases for 1943, Proc. Staff Meet., Mayo Clin. **19**:602-605, 1944.

428. Winkelstein, A.: Ulcerative Colitis, J. Mt. Sinai Hosp. **11**:159-163, 1945.

429. de Castro Barbosa, J.; Bargen, J. A., and Dixon, C. F.: Regional Segmental Colitis, Proc. Staff Meet., Mayo Clin. **20**:134-143, 1945.

to therapy the conclusion is reached that all such patients should receive an adequate medical regimen, that resection is probably the treatment of choice, that the time of such resection must be carefully determined by the clinician and the surgeon working together, that adequate preoperative management is of the greatest importance and that short circuiting operations do not yield final good results.

The similarity between the red, turgescent, friable mucosa of the bowel in ulcerative colitis and the skin around the site of an ileostomy or a duodenal fistula resulting from enzymatic digestion suggested to Portis, Block and Necheles [430] that enzymatic factors might be operative in ulcerative colitis. The rectal discharge of such patients was found to contain moderate amounts of trypsin. Perfusion of the colon of a dog with trypsin solution led to irritation, hemorrhage and a large increase of mucus. Sodium lauryl sulfate, Abbott (sodium-lauryl-myristal-cetyl and stearyl sulfates, containing 50 per cent sodium sulfate) promoted the healing of cutaneous wounds in animals and in man, but the oral ingestion of detergents did not regularly reduce the enzyme content in the ileal discharge of 9 patients who had undergone ileostomy. [The reviewers find themselves unable to accept this interesting hypothesis until more satisfactory evidence is presented.]

Martin [431] reports extensive thrombosis of the abdominal aorta, the right and left common iliac arteries and the left renal arteries, and infarcts of the kidneys, the spleen, the pancreas and the myocardium arising from mural endocarditis complicating extensive chronic ulcerative colitis.

Bargen and Sauer [432] in an excellent article on ulcerative colitis and carcinoma refer to Bargen's paper of 1929 reporting a 10 per cent incidence of polyposis in 693 cases of chronic ulcerative colitis and an incidence of carcinoma of 2.5 per cent. The present paper is an analysis of 30 additional cases, bringing the total number of cases of chronic ulcerative colitis complicated by carcinoma at the Mayo Clinic to 54. Only 3 of the patients were over 35 years of age at the time of the onset of the colitis. The shortest interval between the onset of the disease and the appearance of symptoms suggesting carcinoma was four years; the longest, forty-two years. In 9 of the 30 cases multiple carcinoma was found, most of the lesions being of the higher grades of malignancy. Sipman [433] reports ulcerative colitis with polyposis com-

430. Portis, S. A.; Block, C. L., and Necheles, H.: Studies on Ulcerative Colitis and on Some Biological Effects of Detergents, Gastroenterology **3**:106-113, 1944.

431. Martin, M. E.: Arterial Thrombosis Associated with Chronic Ulcerative Colitis, Am. J. Digest. Dis. **12**:85-88, 1945.

432. Bargen, J. A., and Sauer, W. G.: The Association of Chronic Ulcerative Colitis and Carcinoma, Clinics **3**:516-534, 1944.

433. Sipman, H.: A Malignant Tumor Developing in a Defunctioned Colon of Twenty Years Standing, Clinics **3**:1059-1061, 1944.

pletely asymptomatic for eighteen years, following permanent cecostomy. An anaplastic carcinoma of the rectum was found on proctoscopic examination and later resected.

Bargen [434] reviews the therapy of ulcerative colitis and reports that the effect of phthalylsulfathiazole was good in 26, fair in 1, slight in 1 and not apparent in 9. The toxicity seems less than that of many drugs commonly used in intestinal diseases.[435] Poth and Ross [436] found that phthalylsulfathiazole is twice as effective as succinylsulfathiazole in altering the coliform flora of the bowel in man. The drug has low toxicity and is well tolerated by patients with ulcerative colitis. Pollard [437] found no "significant amount of sterilization of the bowel" but did think that succinylsulfathiazole produced "a definite and at times dramatic clinical response in three fourths of the thirty-six patients." Bargen [438] considers succinylsulfathiazole and azosulfamide most effective in nonspecific ulcerative colitis, sulfathiazole of value in venereal lymphogranuloma and succinylsulfathiazole most promising in regional colitis. All have been used with indifferent success in regional enteritis. In summary, the results are relatively satisfactory in a few conditions and disappointing in others. Collins [439] concludes that "sulfonamides have a place in the treatment of ulcerative colitis but we do not know which patient will be benefited." Azosulfamide or sulfadiazine or the two combined are preferred in cases of toxic disease; succinylsulfathiazole, in early stages of nontoxic disease.

In 145 cases of idiopathic ulcerative colitis 11 acute perforations occurred, followed by peritonitis and rapid death. The incidence of perforation was 7 per cent; the mortality, 100 per cent. Seven were primary in the colon and 4 in the ileum, following operative procedures.[440]

Garlock [441] considers surgical treatment to be in order for ulcerative colitis in the presence of uncontrollable hemorrhage, profound toxemia

434. Bargen, J. A.: The Medical Management of Ulcerative Colitis, J. A. M. A. **126**:1009-1013 (Dec. 16) 1944.

435. Bargen, J. A.: Sulfathalidine in Intestinal Diseases, Proc. Staff Meet., Mayo Clin. **20**:85-87, 1945.

436. Poth, E., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, J. Lab. & Clin. Med. **29**:785-808, 1944.

437. Pollard, H. M.: III. The Clinical Use of Succinyl Sulfathiazole in Chronic Ulcerative Colitis, Gastroenterology **4**:4-8, 1945.

438. Bargen, J. A.: The Sulfonamide Compounds in Treatment of Diseases of the Intestine, M. Clin. North America **28**:811-824, 1944.

439. Collins, E. N.: IV. Late Results in Ulcerative Colitis, Gastroenterology **4**:8-10, 1945.

440. Jankelson, I. R.; McClure, C. W., and Sweetsir, F.: Idiopathic Ulcerative Colitis: Perforation of the Bowel, Rev. Gastroenterol. **12**:31-37, 1945.

441. Garlock, J. H.: Further Experiences with the Surgical Treatment of Intractable Ulcerative Colitis, New York State J. Med. **45**:1309-1312, 1945.

not responding to medical treatment, impending perforation, polypoid degeneration, extensive scarring and retrovaginal fistula. Ileostomy is indicated in all, followed by graded resection of the colon in the last three groups.

Ileostomy was the primary operation in 38 patients, with 6 deaths, a mortality of 15.7 per cent. Five of the remaining 32 were subjected to subtotal colectomy followed by abdominoperineal resection of the rectum, with no deaths. In 21 of the 38 patients with ileostomy subtotal colectomy was carried out without removal of the rectum. There were 4 deaths, a mortality of 19.9 per cent, peritonitis being the most common cause of death. An ileorectal anastomosis was made in 6 of the 17 remaining patients. Three are alive and are progressing favorably after two, three and five years, respectively; 3 died. Of 6 undergoing primary transverse colostomy for left-sided disease, colectomy on the left side and abdominoperineal resection were carried out in 5, and colectomy on the left alone only in 1, with 1 death. In 13 of another group with primary ileoproctostomy or ileosigmoidostomy and exclusion of the diseased bowel, followed by subtotal colectomy in one stage, there were no postoperative deaths; 11 of this group are progressing favorably, with follow-up studies of nine months to seven years. Of 10 patients with segmental colitis, ileosigmoidostomy was done in 7, with 2 postoperative deaths. The 5 survivors are doing well. In the series of 146 patients who underwent major operations there were 8 in whom acute intestinal obstruction occurred at varying times after they were discharged from the hospital, with death resulting from the obstruction in 5.

During an eight year period Cave [442] operated on 92 persons, 18 of whom died, an operative mortality of 19.5 per cent. During the first two years emergency operations were performed on 15 patients whose disease was in the acute fulminating stage, 8 of whom died, an operative mortality of 53 per cent. In an elective group of 50 patients treated by ileostomy there were 4 deaths, an operative mortality of 8 per cent. The principal indication for emergency operation is perforation. Cave advocates ileostomy followed in six months by subtotal colectomy for patients not responding to medical management.

Of 82 patients with ulcerative colitis, 57 were treated conservatively, with 16 deaths (28 per cent), and 25 surgically with 3 deaths (12 per cent). Dennis [443] emphasizes the psychiatric aspects of the disease and suggests that early ileostomy may offer the most effective therapy.

442. Cave, H. W.: Surgical Experiences with Ulcerative Colitis, S. Clin. North America **25**:301-306, 1945.

443. Dennis, C.: Surgery in Relation to Chronic Non-Specific Ulcerative Colitis: Experience at the University of Minnesota Hospitals, Minnesota Med. **28**:228-234, 1945.

The second edition of "Cancer of the Colon and Rectum" is another standard work to be recommended but not reviewed here.[444]

(*i*) Benign and Malignant Tumors: Browne and McHardy [445] discuss submucosal lipoma of the colon, 130 cases of which have been collected from the literature.

Atwater and Bargen [446] in an excellent paper trace the pathogenesis of intestinal polyps from the earliest epithelial change to frank carcinoma. In 241 consecutive necropsies polyps were found in 166, an incidence of 69 per cent. In accord with the concept of the malignant degeneration of benign polyps is the report by Berson and Berger [447] of 13 cases each with two independent cancers and 3 cases each with three malignant growths. The frequency of multiple cancer was found to be 4.6 per cent. In a survey of the literature, beginning with 1932, they collected 66 cases with two and 6 cases with three cancers. Bacon and Gass [448] describe 5 cases of multiple primary cancer of the rectum and sigmoid colon. An average of 8.8 cases of this type are reported in the literature each year. Murray [449] reports the coincidence of a mother and her son coming to his office on the same day, each with multiple adenoma of the sigmoid undergoing malignant change.

Oppenheimer [450] recommends the use of small amounts of opaque material (30 to 60 cc.) for the diagnosis of early small neoplastic lesions of the rectum, and Whitehead [451] advocates proctoscopy as a routine measure to precede the administration of the barium sulfate enema. Christianson [452] calls attention to certain difficulties in the visualization of rectal lesions on proctoscopy, particularly in that of prolapsing pedunculated tumor of the sigmoid, and emphasizes the importance of the routine proctoscopic examination. The technical difficulties of

444. Rankin, F. W., and Graham, A. S.: Cancer of the Colon and Rectum, Springfield, Ill., Charles C Thomas, Publisher, 1939.

445. Browne, D. C., and McHardy, G.: Submucosal Colon Lipomas: Case Report; Mucocele of Appendix as Complication, Clinics **3**:622-629, 1944.

446. Atwater, J. S., and Bargen, J. A.: The Pathogenesis of Intestinal Polyps, Gastroenterology **4**:395-408, 1945.

447. Berson, H. L., and Berger, L.: Multiple Carcinomas of the Large Intestine, Surg., Gynec. & Obst. **80**:75-84, 1945.

448. Bacon, H. E., and Gass, O. C.: Multiple Primary Malignant Neoplasms of the Rectum and Sigmoid Colon: Report of Five Additional Cases, Am. J. Surg. **68**:240-249, 1945.

449. Murray, F. H.: Multiple Adenomata Undergoing Malignant Changes in Mother and Son, Clinics **3**:1035-1038, 1944.

450. Oppenheimer, A.: Roentgen Diagnosis of Incipient Cancer of the Rectum, Am. J. Roentgenol. **52**:637-646, 1944.

451. Whitehead, L. J.: Roentgenological Manifestation of Malignancy of the Colon, South. M. J. **38**:85-89, 1945.

452. Christianson, H. W.: Prolapsing Tumors of the Rectum and Sigmoid, Clinics **3**:1023-1034, 1944.

demonstrating polyposis of the colon are illustrated in 2 brief case reports.[453] Womack[454] stresses the fact that the gross appearance of rectal adenoma may give a true indication of the degree of malignancy, whereas the histologic study of the portion removed for biopsy may fail to do so. The importance of securing for biopsy a specimen including a portion of the base of the lesions is emphasized. Complete extirpation of all benign lesions is advised.

In 1942 the population of Greater New York was 7,300,000. During that year 1,962 persons died of cancer of the stomach, 1,616 of cancer of the colon and 911 of cancer of the rectum. The combined death rate for cancer of the colon and the rectum was 2,527, or 600 more than the rate for cancer of the stomach.[455]

The location of 778 carcinomas of the large intestine operated on at the Mayo Clinic in 1943 was as follows: rectum, 32 per cent; sigmoid, 28 per cent; rectosigmoid, 12.5 per cent; descending colon, 7.4 per cent; cecum, 5.5 per cent; transverse colon, 4.1 per cent; ascending colon, 3.6 per cent; splenic flexure, 3.2 per cent; hepatic flexure, 2.7 per cent; anus, 0.4 per cent.[456]

In an analysis of data on acute obstruction due to carcinoma of the colon, Gruenfeld[457] points out that about 20 to 30 per cent of patients with such involvement of the colon (rectum and rectosigmoid excluded) suffer an attack of complete (acute) obstruction. Complete obstruction with meteorism endangers the viability of the cecum. Decompression by colostomy is advised, followed by resection of the tumor-bearing area. Finn and Lord[458] report the successful removal without miscarriage of a carcinoma of the colon which produced acute intestinal obstruction during pregnancy.

A carcinoma of the sigmoid with an intercolic fistula extending to the transverse colon and an external fistula with abscess formation, requiring resection of the transverse colon, splenic flexure, descending colon and sigmoid, is reported by Gratiot and Nunes.[459]

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453. Schutte, A. G.: Difficulties in Roentgenographic Diagnosis of Polyposis of the Colon, Clinics **3**:1039-1044, 1944.

454. Womack, N.: Adenoma of the Rectum, S. Clin. North America **24**: 1143-1150, 1944.

455. Heyd, G.: The Curability of Cancer of the Large Bowel, Rev. Gastroenterol. **12**:23-30, 1945.

456. Bargen, J. A.: Annual Report on Intestinal Diseases for 1943, Proc. Staff Meet., Mayo Clin. **19**:602-605, 1944.

457. Gruenfeld, G. E.: Acutely Obstructing Carcinoma of the Colon, S. Clin. North America **24**:1126-1142, 1944.

458. Finn, W. F., and Lord, J. W., Jr.: Carcinoma of the Colon Producing Acute Intestinal Obstruction During Pregnancy, Surg., Gynec. & Obst. **80**:545-548, 1945.

459. Gratiot, J. H., and Nunes, A. J.: Combined Intercolic and External Fistula Caused by Carcinoma of the Sigmoid, Am. J. Surg. **66**:265-268, 1944.

In a statistical discussion Pemberton and his associcates [460] point out that the mortality from operations on the large intestine was 13.1 per cent in 1933, while it was 3.3 per cent in 1943. The chief cause of death continues to be infections, 50 per cent of which are peritoneal. Coller and Vaughan [461] report 173 patients with carcinoma of the colon treated by operation. In 60 of the lesions of the ascending colon, the mortality was 6.6 per cent; in 21 of the transverse colon, 23.8 per cent; in 9 of the splenic flexure, 11.11 per cent; in 13 of the descending colon, no mortality, and in 70 of the sigmoid, 4.2 per cent mortality. Eighty-three per cent of lesions were considered resectable. The mortality from resection was 4.1 per cent and the over-all mortality 7.5 per cent. In a group of 110 patients with colonic carcinoma (exclusive of the rectum and the sigmoid), 85 resections (77.3 per cent) were performed. The high rate of resectability is attributed to the increasing use of primary closed resection in the descending (left) colon. In the hands of White and Amendola [462] the mortality rate from closed resection was one half that from the Mikulicz type of resection. Babcock and Bacon [463] in an analysis of 712 operations conclude that the tendency is toward a wider use of end to end resection, the preservation of the uninvolved anus and the elimination of the Mikulicz operation except when serious peritoneal contamination renders a rapid termination of the intra-abdominal procedure desirable.

Pfeiffer and Levering [464] in analyzing 179 cases found that in 108 the tumor was located in the rectum or the sigmoid and that in almost 50 per cent of this group it could be found by digital rectal examination. One hundred and sixty-four patients were operated on (91.6 per cent operability), and the growth was resected in 106 of these (64.6 per cent). The postoperative mortality was 20.1 per cent, although in favorable cases it was only 5.5 per cent. In 256 cases studied by Bacon and his associates [465] the cancer was resectable in 208 (81.2 per cent).

460. Pemberton, J. deJ.; Dixon, C. F.; Waugh, J. M., and Black, B. M.: Annual Report of Surgery of the Large Intestine for 1943, Proc. Staff Meet., Mayo Clin. **19**:605-612, 1944.

461. Coller, F. A., and Vaughan, H. H.: Treatment of Carcinoma of the Colon, Ann. Surg. **121**:395-411, 1945.

462. White, W. C., and Amendola, F. H.: The Advantages and Disadvantages of Closed Resection of the Colon, Ann. Surg. **120**:572-581, 1944.

463. Babcock, W. W., and Bacon, H. E.: Complications in the Surgical Treatment of Carcinoma of the Large Bowel, J. A. M. A. **128**:73-77 (May 12) 1945.

464. Pfeiffer, D. B., and Levering, J. W.: Carcinoma of the Large Bowel: A Review of Cases Treated by the Pfeiffer Surgical Clinic over a Five-Year Period—1939 to 1943 Inclusive, Clinics **4**:27-35, 1945.

465. Bacon, H. E.; Gass, O. C., and Todhunter, W. D.: The Present Status of the Surgical Treatment of Cancer of the Rectum and Pelvic Colon, Clinics **3**:982-986, 1944.

The operative mortality from resection was 7.6 per cent. Metastases were found in the liver in 8.4 per cent and in regional lymph nodes in 37.2 per cent. Cole [466] reports 50 consecutive cases of carcinoma of the colon. Partial or complete obstruction occurred in 60 per cent of the cases of tumor of the descending colon; the operative mortality was 32 per cent. Obstruction occurred in 16.6 per cent of those involving the ascending colon, with an operative mortality of 10 per cent.

Poth [467] discusses the importance of the preoperative administration of sulfonamide drugs. The results obtained when succinylsulfathiazole and when phthalylsulfathiazole was used are compared. The former gave a better mechanical cleansing, due to the more fluid feces. Ten years ago the mortality from primary surgical treatment of the colon was 10 per cent; today with good preoperative and postoperative care, including the administration of sulfonamide drugs, the mortality has been reduced to 2 per cent. A coliform count of 1,000 organisms per gram of feces is considered adequate. The usual dosage of succinylsulfathiazole was 0.02 Gm. per pound of body weight every four hours or 3.0 Gm. every four hours for an average-sized man of 150 pounds (68 Kg.) (approximately 0.25 Gm. per kilogram of body weight). The corresponding dose of sulfathalidine is 1.5 Gm. every four hours.

Dixon and Benson [468] report that in cases of closure of a colonic stoma infection of the operative wound occurred in 84 per cent and a fecal fistula developed in 30 per cent of a series of 102 cases in which no sulfonamide compound was employed, whereas infection of the wound occurred in only 13 per cent and a fecal fistula in only 2 per cent of 102 cases in which a combination of succinylsulfathiazole and sulfathiazole was administered. In Behrend's [469] hands the preoperative use of succinylsulfathiazole has reduced the hospital stay of patients undergoing operation on the colon from an average of 65.1 days to 27.4 days by allowing resection with end to end anastomosis to be substituted for the Mikulicz operation.

Emmett and Cristol [470] report 33 cases in which resection of the rectum or the sigmoid complicated by obstruction of the vesical neck

466. Cole, W. H.: Carcinoma of the Colon, Rocky Mountain M. J. **42**:169-178, 1945.

467. Poth, E. J.: Succinylsulfathiazole and Phthalylsulfathiazole in Surgery of the Colon, Surgery **17**:773-780, 1945.

468. Dixon, C. F., and Benson, R. E.: Closure of Colonic Stoma: Improved Results with Combined Succinylsulfathiazole and Sulfathiazole Therapy, Ann. Surg. **120**:562-571, 1944; Tr. Am. Surg. A. **62**:562-571, 1944.

469. Behrend, M.: Colon Surgery and the Sulfonamide Drugs with Especial Reference to the Elimination of the Mikulicz Operation, J. A. M. A. **128**:9-12 (May 5) 1945.

470. Emmett, J. L., and Cristol, D. S.: Urinary Retention Following Surgical Operation on the Rectum and Sigmoid, J. A. M. A. **126**:1077-1079 (Dec. 23) 1944.

did not respond to the usual medical measures. Transurethral resection of the prostate resulted in excellent results in 30, poor in 2 and fair in 1.

Tilton [471] describes a 73 year old woman with an inoperable tumor, which was found to be a lymphosarcoma.

Squamous cell carcinomas comprise about 5 per cent of the malignant tumors of the anus and the rectum; the remainder are almost all adenocarcinomas. Of 40 squamous cell carcinomas, 34 occurred in females and 6 in males. Thirty-nine of these tumors could be palpated on digital examination. Anal fissure is often confused with squamous cell carcinoma. Inguinal metastases occur not infrequently. The tumor grows slowly and can be treated either by surgical resection or irradiation. Seven of 40 patients survived five years or more clinically free of cancer.[472]

Bacon and Pena [473] present 2 cases of malignant melanoma of the anorectum, emphasizing the extreme malignancy of the tumor.

Yaker [474] reports a carcinoid of the rectum and discusses the difficulties of pathologic diagnosis. The rarity of the lesion is shown by the fact that Stout found only 12 cases reported in the literature.

Jackman and Buie [475] excised submucosal rectal nodules of varying size, which were found just proximal to the dentate margin; 59.5 per cent were chemical in origin, following treatment by injection; 4.2 per cent were carcinoids; 4.2 per cent, lymphosarcoma; 10 per cent, benign tumors (fibroma, lipoma, leiomyoma), and 21.1 per cent were inflammatory.

(*j*) Syphilis and Lymphopathia Venereum: An unusual case of syphilis with rectal stricture is reported by Melamed and Feld.[476] The Frei test was repeatedly negative, and the lesion improved remarkably under antisyphilitic therapy.

Woods and Hanlon [477] analyze data on 192 inflammatory strictures of the rectum. In 86 per cent of 105 cases in which tests with lympho-

471. Tilton, B. T.: Carcinoma and Lymphosarcoma of the Colon: A Case of Lymphosarcoma of the Descending Colon, Am. J. Surg. **66**:300-308, 1944.

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pathia venereum antigen were made positive reactions were obtained. Various methods of treatment were used, with inconclusive results. Thirty-five patients underwent resection of the rectosigmoid, with no deaths. David, in the discussion, mentions marked improvement or cure in many such patients from the use of the sulfonamide drugs, but concludes nevertheless that resection is indicated for dense fibrous strictures.

(*k*) Irradiation Injury: McIntosh and Hutton [478] report 44 cases of temporary or permanent stricture of the bowel following irradiation of carcinoma of the cervix. In 33 the process was confined to the pelvic colon and the rectum. Severe and extensive irradiation injury of the bowel may undergo healing with little or no functional impairment in spite of marked anatomic narrowing. Careful medical treatment, consisting of a bland low residue diet and the use of antispasmodic drugs, is of value. Black and Waugh [479] report segmental resection of such a stricture.

(*l*) Foreign Bodies: Akcakoyunlu [480] reports that a 40 year old woman spontaneously passed through the rectum a Kocher forceps left within the peritoneal cavity at a gynecologic operation fourteen months earlier.

(*m*) Congenital Anomalies: Lee [481] presents an analysis of 16 cases to emphasize the high frequency with which fistula between the rectum and the genitourinary tract is associated with deformity of the lower part of the rectum.

(*n*) Pruritus Ani: McCutchan [482] concludes that pruritus ani is a symptom complex and not a disease.

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478. McIntosh, H. C., and Hutton, J. E.: Clinical and Roentgen Aspects of Irradiation Stricture of the Rectum and Sigmoid: Its Course and Treatment, Am. J. Roentgenol. **52**:647-662, 1944.

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News and Comment

GENERAL NEWS

Twenty-Fifth Anniversary of the Discovery of Insulin.—The twenty-fifth anniversary of the discovery of insulin will be observed with a program in Convocation Hall, at the University of Toronto, on September 16. Many internationally known figures in the field of medicine will be present to honor the occasion. Among them will be R. D. Lawrence, physician in charge, Diabetic Clinic, King's College Hospital, London, England; H. C. Hagedorn, Gentofte, Denmark; Bernardo A. Houssay, Research Institute of Experimental Biology and Medicine, Buenos Aires, Argentina, and Elliott P. Joslin, Harvard Medical School, Boston. This observation will be followed by the regular annual meeting of the American Diabetes Association.

On September 23 Eli Lilly and Company will sponsor an International Diabetes Clinic to be held at the Indiana University Medical Center in Herty Hall of the State Board of Health Building, Indianapolis. International importance will be given to this meeting by the presence of Professor Charles H. Best, Toronto, Canada, co-discoverer with Banting of insulin, Professor Houssay, Dr. Lawrence and Dr. Hagedorn. They will discuss various phases of diabetic care.

Book Reviews

Experimental Studies on the Vasomotor Innervation of the Retinal Arteries (Tr. by Robert Fraser). By Kaj Robert Porsaa. Price, 10 Danish kroner. Pp. 201, with 55 illustrations. Copenhagen: Einar Munksgaard, 1941.

Much interest and some controversy have arisen in the past over the question as to whether or not the retinal arteries and those of the brain behave physiologically alike in all respects. The author by carefully controlled and ingenious experiments has probably demonstrated that they do.

The experimental work, that is carefully detailed, had for its objective the elucidation of the vasomotor innervation of the retinal arteries and the relation of this innervation to the circulation in the other parts of the organism, particularly in the brain. It showed, among other things, that the retinal arteries are not directly controlled by the vasosensory nerves and are not subject to the regulation of the universal circulation. In fact, the retinal arteries, in the experiments, behaved precisely as do the cerebral arterioles of the same order of magnitude.

One of the most interesting chapters is that having to do with the relation of the retinal arteries to experimentally produced variations in blood pressure by compression of the abdominal aorta, drugs, faradic stimulation of the depressor nerve, diminution of the intravascular blood volume and inhibition of the heart action.

This work, therefore, is not without some clinical importance to the internist, physiologist, neurologist and ophthalmologist. It will bear their careful attention.

The Cookery Book for Diabetics. Compiled by The Diabetic Association, 9 Manchester Square, London, W. 1. With a foreword by Prof. V. H. Mottram. Price, 4s. Pp. 82, with illustrations. London, England: H. K. Lewis & Co., 1945.

"First Lessons in Food Values" and "Hints for Diabetic Cookery," as presented in the first few pages of this book, are well worth reading for the diabetic patient, the dietitian and the physician. Here is a clear and simple explanation of what can be a difficult subject for the average patient. The data on rationed foods and many of the recipes, being typically English, will not interest the American diabetic patient. However, the recipes for salads and for desserts might be helpful. They are arranged as to carbohydrate value; amounts vary from 0 to 20 Gm. of carbohydrate per serving. In order to use these recipes to his advantage the patient with diabetes would have to be familiar with making substitutions.

Cornell Conferences on Therapy. By Harry Gold, M.D. Volume 1. Price, $3.25. Pp. 322. New York: The Macmillan Company, 1946.

A great many doctors have read with interest and profit the "Cornell Conferences on Therapy" as they appeared in the *New York State Journal of Medicine.* It is therefore a satisfaction to have some of these authoritative discussions available in book form.

Among the fifteen topics selected for volume 1 is a variety of subjects, including five on various aspects of heart disease. Aside from the "regulars"—Dr. Gold, Dr. Cattell and others—some guest specialist usually participates and the presentation of part of the discussion in the form of a dialogue adds vivacity and "punch" to what is said.

The book makes for good reading and will be most useful as a reference. One wonders whether an index would not have been worth while.